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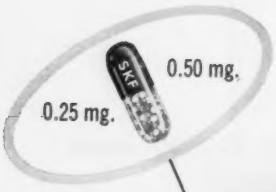

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Cerebral Vascular Insufficiency

An Explanation of the Transient Stroke

ELIOT CORDAY, M.D.
SANFORD ROTHENBERG, M.D., Los Angeles
and
STANLEY MARTIN WEINER, M.D., Denver

Acute cerebral vascular insufficiency may be defined physiologically as a deficiency of cerebral arterial blood flow resulting from an inadequate systemic arterial blood pressure or impairment of the cardiac output.[1] This condition is often transient and correctible, although the resulting deleterious effect upon the brain may or may not be permanent. The deficit in cerebral blood flow may involve the whole brain, or it may be localized. When it is generalized, the well-known symptoms of syncope, generalized grand mal seizures, etc. may occur. It has not been clearly recognized, however, that focal cerebral manifestations, such as hemiplegia, hemisensory disturbances, and Jacksonian seizures, are not uncommonly the result of localized cerebral vascular insufficiency. In the past, such disorders when permanent have been attributed to cerebral hemorrhage, thrombosis, or embolism. When focal cerebral signs have been transient, they have usually been considered a result of localized cerebral vascular spasm. It is the purpose of this paper to show that many of these clinical phenomena are explainable on the basis of a different mechanism, generalized or localized cerebral vascular insufficiency.

The concept of acute cerebral vascular insufficiency is closely analogous to the concept of acute coronary insufficiency. The latter syndrome, described and popularized by Master and co-workers,[2] occurs when there arises a localized (or generalized) disproportion between the coronary arterial blood flow and the requirements of the myocardium. The coronary arteries, even when narrowed by arteriosclerosis, are usually able to satisfy the demands of the resting heart. But when the requirements of the heart are increased by such factors as effort, tachycardia, or excitement, or when the blood supply is reduced, as in shock or hemorrhage, a functional inadequacy of the coronary circulation may occur. Anginal pain, electrocardiographic changes, and occasionally heart failure may result and persist until the exciting factor is corrected.[3] Friedberg and Horn[4] have demonstrated that an attack of coronary insufficiency, without actual coronary occlusion, may result in myocardial necrosis, especially if the

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Department of Medicine, University of California Medical Center, Los Angeles (Dr. Corday); former resident in Medicine, Cedars of Lebanon Hospital (Dr. Weiner).

coronary blood flow is not promptly restored to an adequate level.

It will be seen that a similar mechanism, cerebral vascular insufficiency, may under conditions of reduced systemic blood pressure give rise to focal cerebral phenomena. These signs and symptoms are often reversible if measures to restore the cerebral blood flow are promptly instituted. But if the condition is unrecognized or neglected, permanent cerebral damage will ensue. Hence the importance of early treatment cannot be overemphasized.

A brief account of cases will serve to illustrate some of the clinical features of cerebral vascular insufficiency. It will be noted that each of these patients developed acute (focal) cerebral disturbances without evidence of vascular occlusion by thrombosis or embolism or of cerebral hemorrhage. In each patient the cerebral disorder was associated with acute systemic hypotension of severe degree or disturbed hemodynamics. Finally, in each patient the presence of cerebral arteriosclerosis either was demonstrated or could safely be assumed.

Report of Cases

Case 1.—A 55-year-old man felt perfectly well all his life until he had right renal colic and passed a stone, at age 50. Angina pectoris had been experienced mildly since age 52, and a myocardial infarction had occurred at age 53. Blood pressure ranged from 180/125 to 160/100. At age 54, he experienced a series of six or more attacks of numbness lasting 5 to 45 minutes, beginning in right knee with spread to right arm and face, accompanied by sweating, giddiness, nausea, and desire to vomit and move his bowels. In only one attack numbness began in the left leg and spread to left face, to right upper lip, to left side of tongue, with inability to speak clearly (tongue moved incoordinately). No headache was experienced with any attack.

Examination.—EEG was normal. Hypersensitive carotid sinus reflex, inhibitory type, was discovered. B. P. arms always a bit less than B. P. legs. Grade II fundi. All peripheral arteries pulsatile. Fluoroscopy: T. D. heart, 17.4 cm. (35%+), left ventricular enlargement, tortuous and unfolded thoracic aorta. Laboratory: Urine, c. b. c. B. U. N., F. B. S., all normal; sedimentation rate normal. Regitine test: negative.

Progress—Angina and severe hypertension were treated by weight reduction, reduced activity, glyceryl trinitrate, pentaerythritol (Peritrate), pentolinium, and rauwolfia. Blood pressure remained high despite therapy. At age 55, one month before he died, bishydroxycoumarin (Dicumarol) was started (and easily regulated) because of angina pectoris decubitus. Two days before death he suffered right flank pain with microscopic hematuria. Prothrombin time was 36%; blood pressure fell to 160/90 (from 250/120 four days before). I. V. urogram was normal eight months before. The pain persisted, and next day temperature reached 100 F. He died suddenly, quietly in bed.

Postmortem Examination.—Old myocardial infarction of the anterior surface of the heart. The anterior descending coronary artery revealed a partially recanulized thrombus. Cut sections of the brain revealed two areas of yellow cystic malacia in the globus palidus and the occipital lobe. The carotid vertebral and cerebral vessels were narrowed by arteriosclerotic process but were patent.

This patient had many attacks of cerebral vascular insufficiency with cerebral infarction, probably due to an inhibitory type of hypersensitive carotid syndrome.

Case 2.—A 62-year-old white woman entered the Cedars of Lebanon Clinic for cholecystectomy for cholelithiasis. She was found to have numerous premature ventricular systoles and had mild congestive heart failure. She was digitalized and, because of an increase in premature ventricular systoles, was given quinidine, 3 grains (0.2 gm.) q. i. d. The digitalis was stopped because a bigeminal rhythm developed, but nevertheless the premature ventricular systoles persisted. Quinidine, therefore, was increased to 9 grains (0.6 gm.) q. 4 h. Sixteen hours later the patient suddenly collapsed and was pulseless and apneic and blood pressure could not be obtained. Physical examination at the time revealed a stuporous aphasic patient with a stiff neck, positive Babinski response on the left. Lumbar puncture was performed because it was thought she had sustained a sudden cerebral hemorrhage. The patient recovered within 12 minutes, and the pulse revealed very frequent premature beats. During the next few hours, the positive Babinski sign and stiff neck cleared and the patient became alert and able to speak but was amnesic for three hours. Approximately 12 hours after the collapse, a tachycardia was noted and an ECG was taken immediately (Fig. 1). While the ECG tracing was being obtained (*B*), which revealed an acute ventricular tachycardia, a grand mal type of convulsion occurred, after which the arrhythmia spontaneously subsided.

It was felt that at this time the ventricular tachycardia might be secondary to the large dose

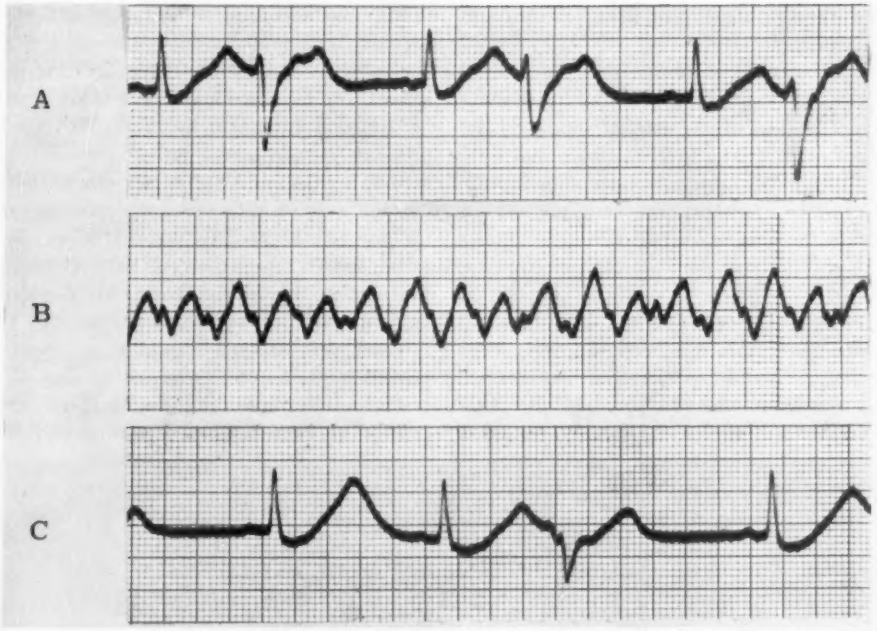

Fig. 1.—ECG's taken (*A*) just before and (*C*) just after a paroxysm of ventricular tachycardia. While ventricular tachycardia (*B*) persisted, the patient revealed transient signs of cerebral vascular insufficiency.

of quinidine which had been administered, so the quinidine was discontinued, and the patient was treated with 250 mg. procainamide I. M. q. 6 h. and then later switched to the same dose orally. Thereafter, she made a complete recovery, and all the neurological signs and symptoms disappeared. Further ECG's showed only rare ventricular premature contractions, and the patient was discharged on the 17th hospital day without surgery. It is concluded that the patient had developed two episodes of cerebral vascular insufficiency due to ventricular tachycardia (References 14 and 15).

CASE 3.—A white man aged 68, who was hypertensive, suddenly lost the sensation of his right leg and within a few minutes was unable to move the extremity. His color had become ashenpale, and his wife stated that he was perspiring profusely but that his skin was icy cold. When seen by a physician 15 minutes later, the patient was found to be in a state of shock. His blood pressure was 65/50. He was pale, and his skin was cold and clammy. He had no sensation in the lower right extremity, and his patellar and ankle reflexes were hyperactive. The plantar response of the right foot was of the Babinski type. His other reflexes were normal. While awaiting an ambulance for transfer to the hospital, the patient vomited a large amount of bright red and dark red blood. The red blood cell count was 3,600,000; the hemoglobin concentration was 65%. This case indeed presented a strange diagnostic problem. Two disturbances were apparent—a cerebral and a gastric event.

The patient received a transfusion of 500 cc. of whole blood within one and one-half hours of the onset of the neurological symptoms. The blood pressure promptly rose to 160 systolic, and the signs of shock disappeared. When the state of shock had been corrected, all the neurological signs and symptoms disappeared. The Babinski response was no longer present.

The diagnosis then became apparent. Cerebral vascular insufficiency had developed owing to the hypotensive state, which resulted from the gastric hemorrhage. The hypotensive state was corrected within one and one-half hours. This resulted in a reversal of the focal cerebral changes, which were secondary to cerebral vascular insufficiency.

Anatomical and Physiological Considerations

The anatomical and physiological considerations pertinent to the development of cerebral vascular insufficiency have been discussed in detail elsewhere.[1] Therefore,

only a brief statement of these features will be presented here.

It is essential to realize that the arterial blood supply of each cerebral hemisphere is independent of the arterial supply of the other. This characteristic applies not only to the carotid system, which supplies the anterior two-thirds of the hemispheres, but also to the vertebral system, which supplies the posterior one-third of the hemispheres. Although a potential collateral circulation through the circle of Willis joins the two hemispheres, this does not function under ordinary conditions. Arterial blood from one hemisphere does not traverse the circle of Willis to the opposite side except when the arterial pressure in the latter is significantly lowered relative to the first side.

The significance of the lack of a dependable collateral blood supply from the opposite hemisphere when the flow through a single cerebral vessel is compromised by disease can be strikingly demonstrated by analogy with the phenomena which occur in a system of rigid tubes. For present purposes only two principles need be recalled: (1) The velocity of flow in a tube of given caliber is proportional to the pressure of the fluid, and (2) the pressure remaining constant, the volume of flow per unit time is proportional to the fourth power of the diameter of the tube, Poiseuille's law (Brew and Dill). Assuming that relationships roughly approximating these are also valid for cerebral vessels, the second principle would mean that if the caliber of an artery were reduced by arteriosclerosis to half its normal value, the volume flow through this artery would be reduced to one-sixteenth its previous level, provided the pressure within the artery were maintained. If the pressure were reduced by any means at all, the reduction in volume flow would be reduced still more drastically. It is thus clear that the combination of localized narrowing in the arterial tree and hypotension can readily lead to severe ischemia of the area supplied by the involved vessel. If the hypotension is severe, the collateral circulation will also fail, thus further endangering the already ischemic region. It is quite possible for an artery narrowed to a moderate extent by arteriosclerosis or by congenital defect to carry on its function satisfactorily when the blood pressure is adequate; but if hypotension occurs, serious, and sometimes irreversible, damage to brain cells may take place unless the pressure is promptly restored to an adequate level. Since cerebral arterial blood pressure is directly proportional to mean systemic arterial pressure, restoration of cerebral pressure must usually be accomplished by systemic measures.

The above considerations support the concept of focal cerebral ischemia, with or without actual infarction, resulting from an excessive hypotension confined to a single artery and its branches. This physiological abnormality, which we term cerebral vascular insufficiency, has not previously been clearly described, nor has much attention been directed toward its experimental elucidation.

The only previous direct experimental investigations of the effects of systemic (and hence, cerebral) arterial hypotension in the presence of occlusive cerebral arterial disease are those which were carried out by Thompson and Smith.[6] These observers occluded the middle cerebral artery in monkeys by means of a clip. When the systemic arterial pressure was maintained at a normal level after this procedure, no clinical, electroencephalographic, or pathological changes could be demonstrated in the experimental animals. However, when, after the middle cerebral artery was clamped, the blood pressure was reduced to half its normal level and maintained at this low level for one hour, signs of hemiplegia consistently developed, associated with distinct electroencephalographic abnormalities, and massive infarcts were found in the distribution of the occluded vessel. These clinical and pathological changes were, furthermore, severe and permanent. In these studies, the development of cerebral infarction would seem to result from inadequacy of the collateral circulation in the

presence of hypotension. On the contrary, when the pressure was maintained at normotensive levels, the collateral blood flow was apparently capable of preventing the occurrence of significant ischemic changes in the region usually supplied by the occluded artery.

Experimental Studies

In each of five monkeys the right internal carotid artery was partially obstructed by means of a Goldblatt clamp. Control electroencephalograms were then obtained from the frontal and temporal areas bilaterally.

A state of systemic, and hence bilateral cerebral hypotension was then produced by bleeding the animals from the femoral artery. The mean blood pressure was reduced to 20-50 mm. Hg (systolic, 40 to 70 mm.) in this manner. When it was desired to restore the blood pressure to a normal level, the same blood was retransfused into the femoral artery, or saline or arterenol was injected. Hypotensive states were produced and corrected three or four times in each animal. During each hypotensive and normotensive phase, new electroencephalograms were made (Fig. 2).

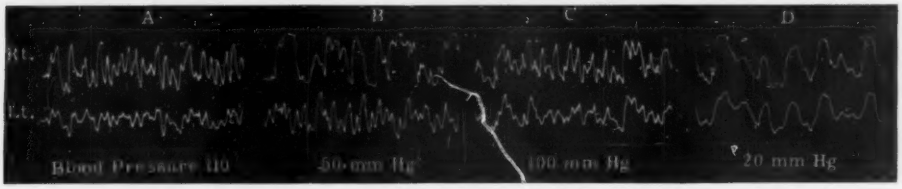

Fig. 2.—EEG's of a monkey whose internal carotid and vertebral arteries were narrowed to one-fifth the original diameter. At normal B. P.'s (*A*) the EEG's are normal; when the animal was bled and B. P. dropped to 50 mm. of Hg (*B*), there was slowing of the waves on the side of the narrowing. When the B. P. was restored (*C*), the EEG's returned to normal. At extreme shock levels (*D*), generalized electroencephalographic changes occurred, as compared to focal changes (*B*).

Results

Using encephalography as a measure of cerebral disturbance, the advent of arterial hypotension in monkeys was shown to result in much more marked abnormalities in the hemisphere whose blood supply had been compromised than in the hemisphere on the normal side (Fig. 2*B*). These exaggerated changes were quickly and completely abolished by restoring the blood pressure to normal levels (Fig. 2*C*). This reversibility was independent of the factor of anemia, since it was evident when the blood pressure was raised by the infusion of saline or a pressor drug (arterenol) as well as by blood transfusion.

These results indicate that the level of systemic and hence cerebral blood pressure plays a crucial role in the maintenance of normal cerebral function in areas of the brain in which the blood flow has been previously compromised. Even in the presence of marked narrowing of a major cerebral arterial channel, the region supplied by this vessel may be able to function satisfactorily provided the blood pressure is normal (Fig. 2*A*). But with the development of a hypotensive state, evidence of dysfunction of this region quickly appears (Fig. 2*B*). If the blood pressure is promptly restored by any method to a normal level, the abnormalities of cerebral function can be rapidly abolished (Fig. 2*C*). The experiments of Thompson and Smith [6] and the experience gained from clinical observation clearly indicate that failure to restore blood pressure promptly will result in irreversible cerebral damage.*

Clinical Aspects

Systemic hypotension of sudden onset may occur in the course of many and diverse conditions. It seems clear that in many instances of sudden systemic hypotension cerebral vascular insufficiency may become manifest. It would appear that focal cerebral phenomena, such as hemiplegia and hemisensory disturbances, are to be expected when localized vascular narrowing [1] or occlusion † by arteriosclerosis or congenital anomaly is present when hypoten-

* References 10 and 11.

† References 5 and 12.

Clinical Applications (Slide)

1. Hypotension due to hemorrhagic shock.
2. Hypotension due to coronary shock.
3. Hypotension due to antihypertensive drugs.
4. Postural hypotension.
5. Hypotension associated with the carotid sinus syndrome.
6. Hypotension due to other vasodepressor phenomena.
7. Hypotension due to surgical procedures and anesthetics.
8. Postsympathectomy hypotension.
9. Cardiac arrhythmias.
10. Congestive heart failure.
11. Pulmonary hypertension.
12. Gravitational states (aviation).

sion occurs. In the absence of cerebral arterial disease and when the hypotensive state is extreme, generalized cerebral vascular insufficiency and generalized cerebral abnormalities are more likely to be observed. Some of the wide variety of conditions in which systemic hypotension can occur is shown in the Table.

Many authors have reported cases in which acute focal or generalized manifestations of cerebral dysfunction have occurred in the absence of occlusion or hemorrhage of a cerebral artery. For example, Cole and Sugarman[5] described a patient with hemiplegia and facial paralysis. This patient died, and at autopsy a fresh myocardial infarct was discovered. The cerebral vessels were markedly sclerotic, but none was obstructed. Grimson and co-workers[7] have reported patients who had recurring episodes of hemiparesis and hemianethesia during the hypotensive state produced by antihypertensive drugs. Transient cerebral disorders have also been reported[8] in association with orthostatic hypotension, hypersensitivity of the carotid sinus[9] and a variety of other conditions characterized by sudden systemic hypotension.‡

The neurological manifestations in some of these cases have been attributed to cerebral vascular spasm. At the present time there appears to be considerable difference of opinion concerning the existence of spasm of cerebral vessels; a discussion of this question is outside the province of this paper.[14] It is suggested, however, that the cases described and cited above are explicable by the concept of cerebral vascular insufficiency without the necessity of postulating the mechanism of spasm.

It is also suggested that the group of cases described by Denny-Brown, with complete occlusion of the basilar or carotid artery,§ may also be best understood on the basis of cerebral vascular insufficiency. These are cases of chronic occlusion of the carotid or basilar arteries. The patient did not manifest signs of cerebral dysfunction except during periods of systemic hypotension, when recurrent focal cerebral signs developed. It would appear that when the systemic blood pressure was normal (or high), adequate function of the collateral circulation took care of the needs of the area whose normal blood supply had been compromised. When systemic blood pressure fell, the collateral circulation failed, and cerebral signs referable to this area appeared. These again disappeared when the systemic blood pressure returned to higher levels.

Summary and Conclusions

The concept of cerebral vascular insufficiency has been offered as an explanation for a variety of hitherto vaguely understood clinical cerebral phenomena. These are characterized by focal (or general) cerebral disturbances when a state of systemic hypotension occurs in persons with whom cerebral arteries are narrowed or occluded. As a result of anatomical and physiological considerations and experimental investigation it is believed that under conditions of systemic hypotension or reduced cardiac output the collateral circulation of the brain fails to supply the requirements of cerebral tissue, whose arterial flow has been previously compromised. If the systemic blood pressure is promptly raised to a normal level, the collateral circulation again be-

‡ Hamilton, K. A.: Personal communication to the authors.

§ References 10 and 11.

comes adequate, and the cerebral signs and symptoms quickly disappear. If the hypotensive state is allowed to persist, permanent cerebral damage will result.

From a clinical standpoint, it is important to recognize the state of cerebral vascular insufficiency because it can be rapidly abolished by restoring systemic blood pressure to normal, while failure to do so promptly will result in serious and permanent cerebral injury.

In considering the differential diagnosis of cerebral vascular accidents, the clinician must add cerebral vascular insufficiency to cerebral vascular hemorrhage, cerebral vascular thrombosis, cerebral embolus, and cerebral vascular spasm.

ABSTRACT OF DISCUSSION

GEZA DE TAKATS, M.D., Chicago: The concept of cerebral vascular insufficiency, first enunciated by Corday, Rothenberg, and Tracy Putnam, in 1953, has been a most fruitful one, since it not only explains a number of poorly understood phenomena but has important therapeutic applications.

To a vascular surgeon, who is frequently confronted with the deleterious effects of sudden hypotension in ischemic extremities, subsisting on stenotic arteries or barely sufficient collaterals, the idea of a critical pressure, below which decompensation of regional circulation occurs, is most logical. Many years ago, with Robbie S. Brunner (*Surg. Gynec. & Obst.* 68:1021, 1939) we advocated the stabilization of blood pressure of patients under spinal anesthesia with phenylephrine (Neo-Synephrine) and have made ourselves unpopular in the operating room by a continuous nagging of the residents and anesthetists to maintain the patient's blood pressure with blood or plasma expanders and not wait for it to fall until something is done about it. While the critical blood pressure in hemorrhagic or neurogenic shock is assumed to be at 80 mm. of Hg in the young, healthy vigorous soldier, it is certainly much higher in the arteriosclerotic, who may need a sytolic pressure of 140 mm. of Hg for safety. Obviously, the level from where the blood pressure falls, the rate of speed with which it falls, and the duration of the low level are factors which will bring about symptoms of ischemia in any part of the body. Thus, in neurogenic, reflex hypotension which occurs, for instance, in the carotid sinus syndrome, dizziness, convulsions, loss of consciousness occur much more readily than if the same level of hypotension develops as a result of hemorrhage over a period of hours.

Now it is generally known that the first line of defense against hypotension is vasoconstriction. Giving a hypotensive drug for this type of vasoconstriction would be folly and would simply deepen shock. Relieving vasoconstriction in a region of critical ischemia with sympathetic paralysis is an entirely different matter. The relief of regional vasoconstriction will not lower systemic blood pressure and will vastly improve circulation even under conditions of hypotension.

In order to elucidate the hemodynamics of hypotension in a previously crippled circulation, the concept of Alan C. Burton's "critical closing pressure" is most helpful (slide). Every vessel has its own intraluminal pressure, below which it closes actively and completely. The higher the tension in the wall and the smaller the size of the vessel, the more readily the vessel closes. Thus a lowering of blood pressure by 20 mm. of Hg may result in a decrease of flow of 80% (Burton, 1953).

We have previously expressed the thought that cerebral circulation follows the same hemodynamic rules as any other regional circulation affected by partial or segmental occlusion and have utilized this line of thinking in the immediate treatment of apoplexy by sympathetic block (*J. A. M. A.* 136:659, 1948; *Ann. Int. Med.* 41:1196, 1954; *Surgery* 38:915, 1955.). When a cerebral vessel is obstructed, collateral circulation can take over and effectively function, provided a certain critical blood pressure is maintained and provided collateral resistance, which is measurably high, is overcome by sympathetic paralysis. In our last report, 55% of carefully selected cases of stroke were benefited from an immediate injection of procaine to the homolateral and a few hours later to the controlateral cervical sympathetic trunk. None were harmed, and the response gave us a prognostic sign as to the degree of recovery to be expected (slide).

In another line of endeavor, namely the lowering of hypertensive levels by splanchnicectomy, one encounters a similar problem. Fowler and I investigated the side-effects of this operation some years ago (*Arch. Surg.* 59:1213, 1949) and found only two transient hemiplegias in our material. This compares favorably with the incidence of massive hemiplegias or peripheral vascular occlusions in hypothermia with hypotension, also with the transient and permanent cerebrovascular phenomena one sees in postural hypotensives who are on hypotensive drugs.

There are many other examples, more obvious to internists, such as the state of hypotension after coronary occlusion, where all persistent hypotension should be looked upon with disfavor. What I should like to emphasize in this discussion is that hypotension with vasoconstriction is more serious

than hypotension with relaxed vessels. The military surgeon has always known the difference between cold hypotension and warm hypotension. To relieve hypotension, blood and plasma expanders are preferable to pressor drugs.

Hypotension with vasoconstriction also favors thrombosis, and the so-called postoperative arterial thrombosis can often be traced to prolonged hypotension on the table. Thromboembolic phenomena, including pulmonary embolism, are also more numerous after hypotensive episodes (Davis, H. E.: *Ann. Surg.*)

If, as they point out, transient strokes are often not thrombotic phenomena, why use anticoagulants in the so-called internal carotid and basilar artery syndromes. Remember the statistics of Hicks and Warren, that in 60% of patients coming to autopsy with the diagnosis of apoplexy, no arterial thrombus can be found. Remember the figures of William Evans, who among 2351 patients coming to autopsy with myocardial infarctions could find no thrombus in the coronaries in 57% of them. As he pointed out, 1358 of the 2351 patients, had they been placed on anticoagulant therapy, would have received an anticoagulant for a clot which could not be demonstrated by autopsy (*Proc. Roy. Soc. Med.* 47:318, 1954).

If I were to stress three points of great clinical interest, which we have maintained right along, (1) do not use anticoagulants to prevent clots which are not present, (2) make use of regional sympathetic paralysis to overcome collateral resistence, which gets higher as the blood pressure falls lower, (3) if you raise pressure to overcome hypotension, use blood transfusion and plasma expanders but not vasopressors.

Drs. Corday and Rothenberg emphasized the concept of cerebrovascular insufficiency. Dr. Maurice L. Lipkis provided data on Case 2. The Charles P. Skouras Foundation, Mr. and Mrs. Philip Raisin, Mr. and Mrs. George Agins, and Mr. and Mrs. E. Cantor gave financial assistance in this project.

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CORRECTION

In the article "The Incidence of Blood Group A in Pernicious Anemia," by Drs. W. P. Creger and A. T. Sortor, in the August, 1956, issue of the ARCHIVES, the values for P (third line, left-hand column, p. 137) should be >0.01 and <0.025.

The Structure of the Respiratory (Terminal) Portion of the Lungs

B. M. FRIED, M.D., New York

When the lungs of man or lower animal are removed from the chest under sterile conditions, they contain no bacteria. Yet a person inhales 12,000 liters of air in 24 hours, taking in enormous quantities of particulate matter and bacteria. What is more, when fine emulsions of pathogenic bacteria are injected into the air sacs by way of the trachea, they are retained and destroyed in the lungs without the occurrence of local disease. Stillman,[1] for instance, found that "pneumococci which have reached the lungs as a result of inhalation usually disappear within a few hours and give rise to no infection." I[2] observed that a dose of pneumococci that kills a rabbit in approximately three days after injection into the blood stream is harmless to an animal when the diplococci have been introduced into the pulmonary parenchyma by way of the trachea. Besredka[3] demonstrated that the anthrax bacillus could be injected into the lungs of rabbits with impunity when the pathogen was brought in contact with the respiratory portion of the lungs via the trachea, provided the extrapulmonary tissues were spared contamination. The bacilli so inoculated were retained and destroyed in the lungs.

The retention of fine emulsions of bacteria in the lungs is of particular interest in connection with the permeability of the lungs. Colin,[4] for example, injected 6 liters of water into the lungs of a horse via the trachea without causing the animal noticeable discomfort. In another experiment he introduced 25 liters of water within six hours with no apparent ill effect. The water was readily absorbed.

Claude Bernard[5] stated: "The mucosa of the lungs differs from the mucous membranes of other organs by its permeability to organic substances. Potassium iodide injected into the lungs via the trachea can be detected in the urine within five minutes; indigo, safranine, and other dyestuffs are readily absorbed through the air spaces, diffused promptly throughout the body, and rapidly eliminated by the usual channels." When vital dyes, such as pyrrol blue or trypan blue, were injected by me into the lungs by way of the trachea, they were found in the urine within a few minutes after the injection.

The lungs have been found to reflect systemic disturbances and anaphylactic and immunifacient processes.

From the standpoint of circulation the lungs are the point of convergence, and matter which happens to enter the blood stream invariably reaches them. Then, too, they are in direct communication with the outside world and receive dust, bacteria, and other particulate matter from the air. The opinion has been expressed that their functions are probably multiple and not confined to gaseous exchange only. It has been stated that very likely their action on lipids is quasisimilar to that of the liver on carbohydrates.[6] It has been pointed out, too, that absorbed albumins and carbohydrates pass directly into the liver, while fatty substances are transported by way of the lymphatics and thoracic duct to the right side of the heart and the lungs. The lungs have also been said to act on sugar[7] and to be involved in the formation of sugar and simultaneously in the destruction of lib-

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erated sugar. The glycolytic action of lung tissue in vitro has been observed to be superior to that of the majority of other tissues, and it has also been claimed that alkaloids are oxidized in the pulmonary parenchyma.

If the metabolic functions of the lungs are under scrutiny, their role in defense has been firmly established, as has been the observation that this function resides essentially in the respiratory (terminal) portion of the lungs, i. e., in the air sacs.

The air sacs, or alveoli, are minute outpocketings of the respiratory bronchioles, tubular structures about 1 mm. in diameter, devoid of cartilagenous plates but provided with a well-developed muscular support. The bronchioles are lined by epithelial cells, the height of which largely depends on the method of removal of the lung from the chest and particularly on the way they were fixed. Usually the cells are visualized as low cuboidal.

The walls of the alveoli, or the septums, are tenuous membranes made up of a fine network of collagen fibers interwoven with capillaries. They contain no lymphatics. Whether the walls are lined by a layer of cells and, if so, the nature of these cells, has been debated for almost a century. No conclusion has yet been reached. The understanding of the fine structure of the alveoli is of importance, for, as stated above, in this structure lies the defensive and in all likelihood also the metabolic mechanism of the lungs.

Experimental Observations

Intratracheal Injection of Mycobacterium Tuberculosis

Infection of the lungs with Mycobacterium tuberculosis [8] was resorted to in this study because the tissue reactions to this bacillus have been well established. It was also deemed of interest to induce a chronic disease of the lungs in order to be in a position to observe it over a protracted period. Finally, since the hematogenous route of infection used in the past was not helpful in solving the problem, the intratracheal route was chosen.

Tubercle bacilli of known pathogenicity, finely emulsified in a physiologic salt solution, were introduced into the respiratory portion of the lungs of rabbits via the trachea. The animals were then killed at intervals from five minutes to several weeks after the infection.

Studies of the lungs revealed that within a comparatively short period after the infection sparse and barely visible cells lying on and within the septums began to grow in size, assuming the morphology of large phagocytic mononuclear macrophages (Figs. 1 and 2). They grew steadily in numbers, so as to cover the septums, and many detached themselves from their sedentary posts on the alveolar walls and moved in ameboid fashion to the interior of the air sacs, forming an exudate consisting of large mononuclear phagocytes (Fig. 3).

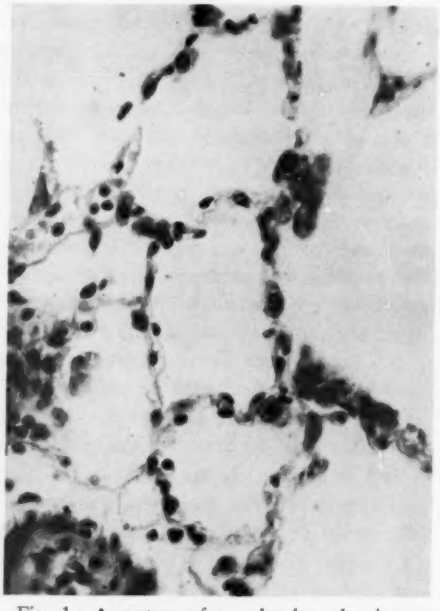

Fig. 1.—A section of an alveolus, showing an early reaction of the alveolar wall cells to the intratracheally injected tubercle bacilli. The increase in number and in size of the cells should be noticed. There is no evidence of the walls being lined by an uninterrupted layer of epithenal cells.

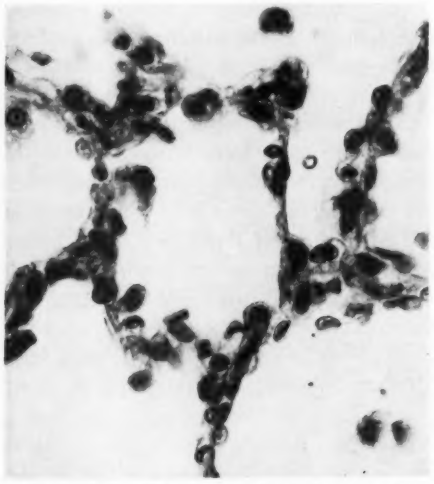

Fig. 2.—A section of an alveolus in the vicinity of a tubercle on the fourth day after the intratracheal injection of tubercle bacilli. The similarity between the sessile and the free cells should be noticed. Some cells are about to abandon their sedentary seat on the septum.

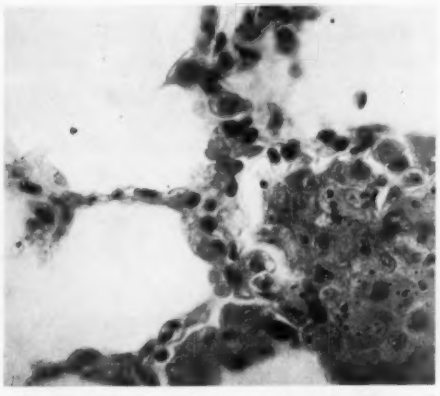

Fig. 3.—Showing densely packed alveolar wall cells filling the air sac in the right lower segment of picture. Also, morphologic changes in the cells alongside the walls and their proliferation.

They phagocytosed tubercule bacilli and in places fused, forming giant cells of the Langhans type.

The earlier stages of the infection were remarkable for a paucity of lymphocytes and granulocytes, so characteristic of hematogenous infection with Koch bacilli. These cells reached the field of inflammation at a later date and to all appearances tended to enforce the indigenous macrophages by transforming themselves into large phagocytes.

Theories on Origin of Large Phagocytes

The site of origin of the large mononuclear phagocytes found in the incipient stages of inflammation in the lungs, particularly in tuberculosis, was the subject of prolonged discussions. Three views were debated: 1. The cells are of hematogenous origin; 2. They originate from the endothelium of the pulmonary capillaries; 3. They are of mixed origin—endothelial and hematogenous. These views, which held sway alternately for decades, were gradually abandoned.

Allen K. Krause [9] wrote: "Added years of uninterrupted observation of the primitive tubercle served only to strengthen the idea of at least one worker, that this parent cell (the epithelioid cell) exists in situ, and, in a thoroughly topographic sense, may be thought of and designated as a fixed tissue cell; that it is not exuded from the blood or lymph, or called as by taxi, from a distance in response to tubercle bacilli."

That the capillary endothelium is the source of the large phagocytic cells in the lungs was described by the late Frank B. Mallory [10] and by Nathan C. Foot,[11] who defined the cells as endothelial leukocytes. Permar,* a disciple of Mallory, wrote: "They (the mononuclear phagocytes) arise, in part at least, if not predominantly, from the fixed endothelial cells of the capillary and subcapillary vessels, in the walls of the atria, sacculi alveolaris and alveoli pulmonis." Foot [11] upheld this concept in many publications, subsequently veered to the theory of this author,† but then turned to the hematogenous idea,[15] which he erroneously

* References 12-14.

† In a letter dated May 27, 1927, Foot wrote to me: "Your paper on the dust cells of the lungs, published in the last number of the *Archives of Pathology* (vol. 3., p. 751, May, 1927) is most interesting and, I think, conclusive. . . . Your conception of the alveolar spaces being naked, except for groups of histiocytes, appeals to me very strongly. . . ."

attributed also to Metchnikoff. Mallory, too, renounced the theory of the endothelial origin of the pulmonary phagocytes (also called dust cells), for his assistants Nye and Parker [16] wrote: "In the past, many writers have claimed that the capillary endothelium in the lungs possesses great phagocytic powers, but few at present hold this view. There is no evidence that the monocytes in the lungs are derived from the circulation or from the capillary endothelium."

The nonparticipation in the early stages of inflammation of cells of hematogenous origin was further demonstrated in studies of inflammation of the lungs in tissue cultures where there was obviously no blood supply.

From the study of the intratracheal infection of animals with M. tuberculosis herein presented it became apparent that the large mononuclear phagocytes (macrophages) originated in situ from the cells lying without and within the alveolar walls, commonly designated respiratory epithelium. The capillary endothelium remained passive, and elements from the circulation were subsidiary late-comers.

Intratracheal Injection of Lipids.—When rabbits are fed in excess with cholesterol emulsified in sunflower oil, with pure cholesterol, or with the yolk of egg, the lipids are invariably phagocytized in the spleen, bone marrow, and elsewhere by proliferated macrophages which store the lipids in their cytoplasms. Because of this trait, they have been designated lipophages. Of interest was the observation that the intima of the blood vessels in the animals so fed became covered with lipids which were deposited within the cytoplasms of large macrophages. (This finding served as a starting point for the studies on the role of lipids in the pathogenesis of atherosclerosis.)

The observation that lipids are a ready prey to macrophages induced me [17] to investigate the cellular response of the lungs to these substances. It was conjectured that if the alveolar wall cells are potential macrophages, as the infection with tubercle bacilli has shown, they would attack the lipids in a characteristic manner.

As in the experiments with the M. tuberculosis, the lipids were introduced into the respiratory (terminal) portion of the lungs via the trachea. Three cubic centimeters of cod liver oil or of liquid petrolatum heated to body temperature was given in a single dose to nonanesthetized rabbits or cats. The animals were killed at different intervals, from about three hours to several days after the injection, and their lungs studied.

As in the infection with tubercle bacilli, the reaction was confined to the cells lying within and without the walls of the alveolar sacs. The so-called alveolar wall cells responded by assuming the morphology and functions of the large phagocytes by rapid proliferation along septums, forming rows of cells, and by abandoning their seats on the walls and migration into the alveolar lumens, forming an exudate of cells containing phagocytized lipids in their cytoplasms, demonstrated by the use of special stains (Fig. 4).

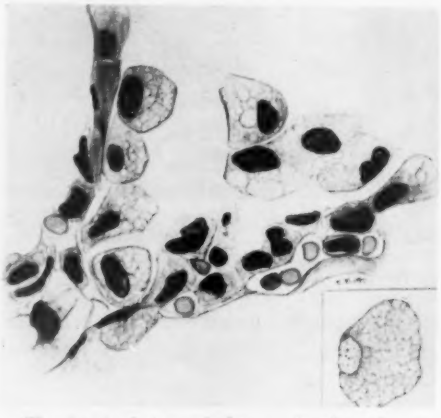

Fig. 4.—A photograph from a drawing of a section of the air sac from a cat injected with cod liver oil via the trachea. The vacuolated (foam) cells alongside the wall as well as those lying free in the lumen are typical macrophages. The cell in the inset, a replica of the alveolar wall cell, is a splenic lipidophage. The difference in the staining of the nuclei is due to differences in metabolic activities.

The response of the lungs to the lipids was a replica of the reaction to enteral and parenteral administration of cholesterol spoken of in the introductory paragraphs. It was a counterpart of the cellular reaction in diabetic lipidemia caused by faulty metabolism of lipids in diabetics. The excess of lipids observed in these cases, as in nephrosis, is taken up by the macrophages, which gorge themselves with the fat, growing in size and in numbers, as demonstrated

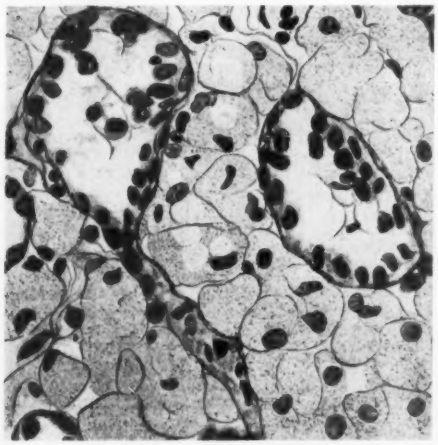

Fig. 5.—A section of the spleen in diabetic lipidemia, showing extensive proliferation and hypertrophy of the cells of the splenic pulp as well as of the sinuses (the littoral cells), which are gorged with lipids.

in Figure 5. The large reticulum cells of the splenic pulp proliferate to such an extent as to completely eliminate other cells. It is of interest that originally the pulp cells of the spleen were looked on as epithelial (Gaucher's disease was considered to be a carcinoma of the spleen—"Primary epithelioma of the spleen," Gaucher), as were the littoral cells lining the sinuses ("Cystic structures lined by epithelial cells").

Lipid Pneumonitis.—A pneumonitis *sui generis* is induced in the lungs by mineral or vegetable oils which have penetrated the alveoli from without (exogenous lipid pneumonitis) or from within (endogenous lipid pneumonitis). The exogenous type was observed in debilitated children or adults in whom the lipids given for medicinal or nutritive purposes entered the trachea and the air sacs. In the endogenous lipid pneumonitis, a pneumonic lesion is induced by lipid substances provided by patients with bronchiogenic carcinoma, lung abscess, or so-called unresolved pneumonia. In both, the exogenous as well as the endogenous, the pulmonary lesion usually results from a combination of the oil and an infection superimposed upon or antedating the accumulation of the oil. The oil fills the air sacs and clogs the bronchioles, inducing lobular or segmental atelectasis, which is instrumental in the loss of the defensive mechanism of the lungs. Bronchial defects invariably affect the lung, which becomes a ready prey to infection. The oil and the pathogens combined yield a complex pathologic picture dominated by the dynamic and destructive pathogens. In the pure lipid pneumonitis, the response to the oil is confined essentially to the cells

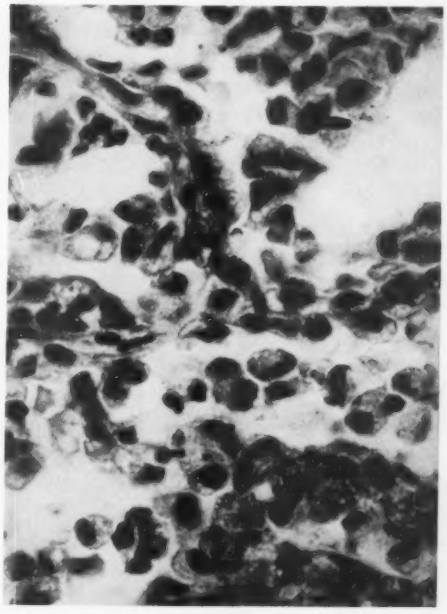

Fig. 6.—Exogenous lipid pneumonitis. Showing morphological and numerical changes in the cells alongside the alveolar walls. Also, the filling of the lumens of alveoli with macrophages. The similarity between the sessile and the free cells should be noticed.

lying in and on the alveolar septums, so-called alveolar epithelium (Fig. 6). It is a counterpart of the experimental pneumonitis caused by the injection of oil into the lungs via the trachea.

Niemann-Pick Disease—Essential Lipid Histiocytosis.—The disease described for the first time by Niemann,[18] in 1914, is a lipid dystrophy afflicting infants. Morphologically it manifests itself in the excessive accumulation of lipids in the body. It differs from Gaucher's disease in the type of lipid, which is a phosphatide, whereas in Gaucher's disease it is a kerasin.‡ As in Gaucher's disease, the spleen and liver are enormously enlarged due to increase in size and proliferation of macrophages, which have phagocytized the lipids and stored them in their cytoplasms.

Abt and Bloom,[21] in a case of Niemann-Pick disease, noticed that in the lungs the lipids were taken up by the cells lying in and on the alveolar walls in a manner similar to the action of the macrophages of the spleen, bone marrow, and subcutaneous tissue. These cells appeared as large foam cells loaded with lipids, resembling the cells observed in the experiments herein reported (Fig. 7).

‡ References 19 and 20.

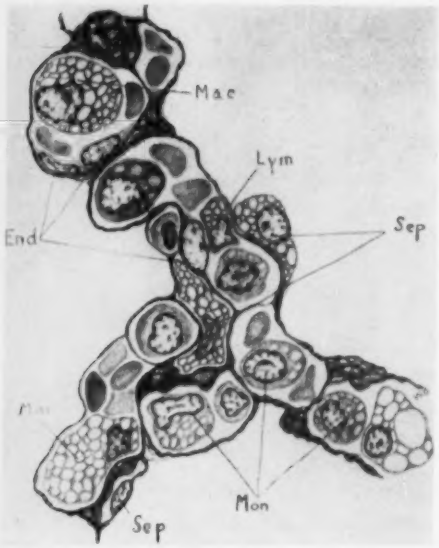

Fig. 7.—The alveolar wall in a case of Niemann-Pick's disease. Mac indicates macrophages; Mon, monocytes; Lym, a vacuolated lymphocyte; Sep, septum cells, resting and mobilizing (Abt and Bloom).

Comment

Whether or not the alveolar walls are covered by cells in an uninterrupted manner has been debated for almost a century. Many observers of the past contended that the walls are altogether devoid of cellular linings, or that they are "nude." A British histologist, Brown, in a letter published in the *Lancet,* in 1874, pleaded: "Will any of your readers kindly inform me where I can obtain a specimen of lung tissue which exhibits squamous epithelium covering the lining of the alveoli?" Subsequently he claimed to have demonstrated the presence of such cells, but, as Brenner remarked: "One wonders what precisely he did see that he designated epithelial scales." In a recent paper Krahl[22] stated: "Concerning the controversy over whether or not the alveolus has a continuous epithelial lining, new evidence is rapidly accumulating which should soon (*sic*) settle this century-old debate."

Above I have quoted Claude Bernard,[5] who found that the mucosa of the respiratory portion of the lungs differs from other mucous membranes by its permeability to organic substances. He observed that when curare was ingested it was not absorbed by the intestinal mucosa and was therefore harmless. He also noticed that the alkaloid remained unabsorbed and innocuous when deposited on the mucosa of the bronchi or bronchioles. However, he was surprised to find that when the alkaloid was pushed into the air sacs it killed the animal as rapidly as if it had been injected into the blood stream. "The extreme tenuity of the septums and the absence of a protective epithelium on their surface," he wrote, "account for this phenomenon."

To histologists of that period it was a matter of pure morphology, but in the years to follow it took on another meaning, in

connection with the new concept of inflammation. Hitherto, inflammation had been considered no more than a local painful episode. With the advent of Metchnikoff's doctrine on phagocytosis, inflammation assumed particular importance in infection and immunity. These were entrusted to the middle embryonic layer, the mesenchyma, and its cellular inhabitants, the macrophages. In fact, today a dominant role is attributed to the macrophages in the metabolism of various substances, such as bile pigments, water, iron, and lipids. The mesenchyma is understood to be not only a "frame," or supporting substance, but an "organ" performing highly differentiated functions. As the mesenchyma and its cells are ubiquitous and their functions quasisimilar, they are looked on as a complex, or a system, the reticuloendothelial system, or, as Metchnikoff suggested, the phagocytic system (*le système phagocytaire* [22a]).

The observations on man and laboratory animals herein discussed have shown that the lungs, too, are endowed with a defensive and metabolic system in no wise differing from other organs. Cells endowed with lurking potentialities characteristic of the mesenchymal ameboid macrophages lie dormant within and without the alveolar walls. Sparse and barely visible under normal conditions, they become conspicuous under pathologic conditions, notably, when bacteria, dust, or lipids penetrate into the air sacs. They are exquisitely sensitive to systemic disturbances. Under the influence of a proper "irritant" they promptly proliferate, grow in size, and detach themselves from the septums to form the intra-alveolar exudate seen in pneumonia or tuberculosis. They form the tubercle in tuberculosis (epithelioid cells) and Boeck's sarcoid and the silicious nodule in pneumonoconiosis, and they are the progenitors of the large foam cells in lipid pneumonitis and the heart failure cells in congestive heart failure. They are the elements that keep the lungs of man and lower animals sterile. They are in all probability the cells described as respiratory epithelium said to line the walls of the air sacs in a syncytial manner.

Whether they are true epithelial cells of endodermal origin which, parodoxically, give rise to wandering phagocytic macrophages or whether they are genuine mesodermal macrophages which procreate cells of their own race is another problem which cannot be adequately discussed here. It is desirable, however, to touch briefly on the problem of the so-called alveolar-cell carcinoma intimately linked with the problem herein discussed.

Alveolar-Cell Cancer.—This type of pulmonary cancer was isolated as a separate entity because of its characteristic pattern which shows virtually normal alveolar walls lined by uninterrupted rows of cuboidal or columnar neoplastic cells, sometimes secreting mucous. The histologic structure is quasiuniform throughout a lobe or a lung and, as no tumor could be visualized grossly in the bronchi, it was assumed (indeed, there was an assumption only) that the cancer arose simultaneously in a multiplicity of foci (so-called multicentric origin) from the cells lining the alveolar walls, the respiratory epithelium. Here then, it was argued, is proof that cells do line alveoli, and they are epithelial, capable of producing an epithelial malignant disease.

Convincing data are at hand to disprove this statement. Indeed, the deductions were made indirectly on advanced cases and in many instances on incomplete autopsies. It has been demonstrated that the picture allegedly characteristic of the alveolar-cell cancer is often observed in cases of abdominal cancers (renal, pancreatic) that had metastasized to the lungs. These cancers reached the lungs via the thoracic duct, right heart, and pulmonary arteries. The neoplastic cells pass the walls of the septal capillaries and cling to the alveolar walls, which they utilize as a supporting substance. They spread from one alveolus to another via the pores of Kohn. A similar picture is provided by a bronchiogenic cancer, as demonstrated in the photomicrograph from

Fig. 8.—So-called alveolar-cell carcinoma. A section from an apical bronchiogenic cancer (superior pulmonary sulcus tumor).

a so-called superior pulmonary sulcus tumor (Fig. 8). The fact that gross tumor was not detected in the bronchus does not negate its existence. It has been repeatedly observed that minute and barely noticeable cancers may yield widespread metastases.[23] Often the primary seat of the cancer cannot be detected. It is even possible that the minute bronchial cancer was healed[24] after an extensive seeding, leaving a scar only, as is the case with malignant teratomas of the testicle. Originally teratomas found in the mediastinal space were invariably diagnosed as primarily mediastinal, whereas now they are generally regarded as metastatic from the testicle, where the growth vanished, leaving a scar. The spontaneous cure of cancer has been reported in the literature. Blades and McCorkle[25] have reported a case of bronchiogenic cancer in a man of 59 that regressed spontaneously.

Complete and thoroughly performed autopsies have demonstrated that the so-called alveolar-cell cancer is either a pulmonary metastasis from a visceral cancer or else the tumor took origin in the epithelium of a terminal bronchiole.[23] In fact, in recent reports the cancer is no longer termed alveolar cell but terminal bronchiolar.

Summary

The lungs are the single visceral organ in contact with the outside world, yet when removed from the chest under sterile conditions they contain no pathogenic bacteria.

The lungs possess a defensive mechanism made up of cells lying on and within the septums. Under pathologic conditions these cells assume the functions of ameboid phagocytic macrophages. These cells also participate in the formation of the tubercle in tuberculosis and Boeck's sarcoid; they produce the elements which make up the silicious nodule in pneumonoconiosis; and they are the progenitors of the large foam cells in lipid pneumonitis and of the heart failure cells in congestive heart failure.

To all appearances these cells are the elements commonly identified as respiratory epithelial cells lining the walls of the air sacs.

1560 Grand Concourse (57).

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Hypertrophic Osteoarthropathy

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Toward the end of the 19th century the clinical entity of hypertrophic osteoarthropathy was first brought to the attention of the medical world. Since that time numerous theories have attempted to explain the mechanisms involved, yet the exact pathogenesis still remains obscure.

Early in the history of this disease, suppurative conditions, such as bronchiectasis, empyema, lung abscess, and pulmonary tuberculosis, were among the principal primary diseases responsible for the arthropathy. As the incidence and severity of these conditions have shown a gradual decline, bronchogenic carcinoma has come to be recognized as the principal cause. This is of prime importance because the signs and symptoms of hypertrophic osteoarthropathy may appear long before the lung lesion can be detected. Therefore, the early recognition of this bone and joint syndrome may be a clue to the earlier diagnosis of the pulmonic lesion, *ergo*, earlier treatment and possible decrease in the over-all mortality rate of cancer of the lung.

Hypertrophic osteoarthropathy may be defined as a chronic proliferative subperiosteal osteitis involving the distal ends of the extremities, manifested by clubbing of the fingers, swelling, pain, tenderness, and accompanying joint disorders. For some time the exact relationship of clubbing of the fingers to the arthropathy was not clear, but the consensus is that hypertrophic osteoarthropathy represents an extension of the process of clubbing and that these related lesions develop secondarily to the same general group of conditions, most commonly those due to chronic pulmonary, pleural, or mediastinal diseases.

It was Hippocrates who first described clubbing of the fingers in empyema. "The fingernails become curved and the fingers become warm especially at their tips. Swelling which come and go are observed in the feet."[1] More than 2000 years later, Pigeaux [2] described clubbed fingers in pulmonary tuberculosis. In 1889 and 1891 Bamberger * reported thickening of the distal ends of the extremities with clubbed fingers in bronchiectasis, pulmonary tuberculosis, and valvular heart lesions. At about the same time, Marie [5] concluded that the bony overgrowth resulted from primary pulmonary disease and was not caused by acromegaly as had been postulated.

Intrathoracic tumors, as a cause of osteoarthropathy, were first mentioned by Brooks [6] and Locke.[7] In 1929, Mills and Mumey [8] reported periostitis and swollen joints in a case of pleural effusion thought to be caused by the Endamoeba histolytica. The significance of the bronchogenic carcinoma found at autopsy was not fully realized, and the authors concluded, "the periosteal lesions were probably on the basis of focal infection from the condition of the lung."

An ever-increasing number of cases due to bronchogenic carcinoma now appeared in the literature,† and the various authors observed that in many cases the bone and joint lesions were present before the diagnosis of lung tumor was established. In 11 cases of "rheumatoid arthritis," Temple and Jaspin [12] found cancer of the lung to be the cause of the arthropathy in six proved specimens. In all cases, improvement or correction of the primary disease

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From Pulmonary Disease Service, Veterans Administration Hospital.

* References 3 and 4.

† References 9-11.

resulted in amelioration of the bone and joint symptoms.

Recent reports have suggested that the incidence of hypertrophic osteoarthropathy may depend on the location of the pulmonary neoplasm. In 13 of their 14 cases, Ray and Fisher [13] found a peripheral type of lung cancer. Others have felt that central necrosis or cavitation of such peripheral lesions may be a contributing factor.‡

Hypertrophic osteoarthropathy has been described in animals, and, as in the human, the primary lesion is usually intrathoracic. Most of the cases reported have occurred in dogs with pulmonary tuberculosis.§ However, recent veterinary literature has also stressed the increasing frequency of bronchogenic carcinoma and other lung tumors as the exciting cause.‖ Mather and Low [21] concluded that canine osteoarthropathy was not associated with metastatic lung involvement, but in a series of four cases, an adenocarcinoma of the perianal gland with metastases to the lungs was described.[22]

Almost all attempts to produce this syndrome in the experimental animal have met with little success. Bamberger injected material from lung abscesses into the rectum of a rabbit. Phemister [23] injected cultures of organisms intravenously. In order to produce intrathoracic conditions which might simulate diseases causing arthropathy, Compere and co-workers [24] injected paraffin into the pleural cavity of dogs and also quoted the work of Harter and Churchill, who tied off the bronchi of cats and monkeys. All their efforts were unrewarded. It remained for Mendlowitz and Leslie ¶ to reproduce hypertrophic osteoarthropathy by anastomosing the left pulmonary artery to the left auricle in dogs. This caused a lesser circuit shunt simulating the conditions seen in congenital heart disease with cyanosis. Shunts from 13% to 45% of the ventricular output resulted, and with the development of osteoarthropathy they noted an increase in the systemic cardiac output, although the blood flow through the lungs remained normal. Mendlowitz [28] also found an abnormally high blood flow in clubbed fingers secondary to heart and lung disease in humans with a reduction in the brachial-digital arterial pressure gradients. This reduction was actually due to an elevated digital arterial pressure. By means of infrared photographs in living patients and postmortem arteriograms, Charr and Swenson [29] demonstrated a local increase in the number and width of the arterioles covering the ungual phalanx of clubbed fingers. Although Lovell [30] agreed there was an increase in caliber of the digital arteries, he attributed the increased peripheral flow to the predominance of arteriovenous anastomoses in this location. Wilson [31] noted the constant relationship between increased blood flow and the development of clubbing, while decreased blood flow resulted in its regression. The fact that capillary pulsation was absent with the increase in peripheral flow supported the belief that the excess blood was diverted through the arteriovenous shunts and bypassed the capillary bed.

But how does the increased flow produce the arthropathy, and how can this condition respond so quickly to corrective treatment of the primary intrathoracic disease? Semple and McCluskie [14] felt that the increased blood flow produced a periosteal hyperemia with a subperiosteal serous effusion in which the new bone was deposited. Similar vascular changes could explain the associated subcutaneous tissue and joint involvement. Barnes and co-workers [32] had shown that widespread vascular hypoplasia existed in arteriovenous aneurysms of the lung. Cudkowicz and Armstrong [33] thought a similar vascular abnormality might be present in hypertrophic osteoarthropathy. They examined the lungs of 15 subjects who had shown various degrees of clubbing due to intrathoracic disease. By injecting a radiopaque medium into these diseased

‡ References 14 and 15.
§ References 16-18.
‖ References 19 and 20.
¶ References 25-27.

lungs they were able to demonstrate occlusion of the major branches of the pulmonary artery in almost all cases. This resulted in the establishment of precapillary bronchopulmonary anastomoses which diverted bronchial blood into the low-pressure pulmonary artery bed distal to the occlusion. Since these anastomoses were not present in normal, healthy lungs and resembled the anastomoses found in clubbed fingers, the authors suggested that the resulting ischemia of the lung set up antidromic impulses in the peripheral pulmonic nerve fibers which reflexly influenced the formation of the arteriovenous anastomoses in the limbs.

Other theories which have been advanced to explain the pathogenesis of osteoarthropathy include the following:

1. The absorption of toxic substances from suppurating foci.
2. The peripheral concentration of toxic products by venous stasis.[34]
3. Peripheral hyperemia caused by the compression of lung capillaries.
4. The formation of toxins as a result of impaired circulation.
5. The anoxic theory received considerable support. It suggested that capillary stasis causing the arthropathy might be due to arterial anoxemia or local anoxia. No explanation, however, could be offered for cases in which there was no demonstrable decrease in oxygen saturation of the arterial blood. Mauer,[35] however, stated that the rouleau formation due to rapid sedimentation rates found in many of the conditions causing clubbing resulted in a low oxygen tension in the tissues. Even though a rapid blood flow was present with a high level of oxygen saturation, the clumped red cells escaped through the arteriovenous anastomoses and produced anoxia by interfering with the gaseous exchange. Branwood[36] thought such an increase in rouleau formation might be due to an alteration of plasma proteins.
6. An endocrine imbalance theory has had many proponents because of the superficial resemblance of osteoarthropathy to acromegaly. In a series of four cases,[37] hyperplasia of the eosinophilic cells of the anterior pituitary was noted in three instances, and in one the pituitary gland was twice the normal size. Bloom[38] found a metastatic nodule in the pituitary from a primary lung neoplasm. Other authors point to the thyroid as a cause, since rare cases of myxedema have been associated with clubbing. The occurrence of gynecomastia in a few cases has also favored an endocrine origin.
7. The elaboration of an osteoblast-stimulating substance by the pluripotential mesothelial cells of pleura has been suggested by Wierman and coworkers.[15]

In spite of the many hypotheses offered, the definite and final answer to the pathogenesis still remains unsolved. Most authors agree that an overnutrition of tissues due to excess blood supply produces the hypertrophy and hyperplasia which are so characteristic of this syndrome and thus corroborate the conclusions of Mendlowitz,[39] who stated, "increased peripheral blood flow will form a cornerstone of future theories on the mechanism of clubbing and hypertrophic osteoarthropathy."

Although this clinical syndrome usually occurs secondary to intrathoracic disease, 3% to 5% of cases may be of the idiopathic variety in which no primary lesion can be demonstrated. This type is characterized by the familial occurrence of marked clubbing of the fingers and toes in healthy young males, associated with increased size and squaring of the extremities due to new deposits of periosteum around the long bones. Another important feature is the marked thickening of the skin of the face, skull, and limbs. The abnormal growth usually starts at about the age of 15 and continues for 7 to 10 years, after which the condition remains stationary. Since the first descrip-

tion by Friedreich,[40] in 1868, the autopsy findings have been reported,[41] the familial incidence verified,# and the redundant skin emphasized.* Various theories as to causation of the generalized periosteal hyperostosis have been propounded, such as a circulating proteinogenic toxin,[46] a constitutional predisposition to a pituitary or hypothalamic factor,[47] or an endocrine origin.[48]

To illustrate the various clinical and roentgenologic manifestations of hypertrophic osteoarthropathy secondary to bronchogenic carcinoma, the following cases are presented.

Report of Cases

CASE 1.—A 36-year-old white man entered the hospital because of swelling of the knees and ankles and a 20 lb. weight loss in the preceding four months. Three weeks prior to admission the fingers and toes showed sudden enlargement. The patient appeared chronically ill, and severe clubbing of the fingers and toes was present. The admitting chest roentgenogram revealed a 3 cm. well-circumscribed density in the right apex. Right pneumonectomy was performed for an adenocarcinoma of the right upper lobe with subpleural extension and metastases to the hilar lymph nodes. Unfortunately, no films were taken of the involved joints, but a mild periosteal proliferation was noted on the lateral aspect of the distal end of the radius (Fig. 1).

Comment.—The characteristic pattern of "acute arthritis" followed by sudden clubbing of the fingers is well demonstrated by this case.

CASE 2.—A 58-year-old man noticed the gradual onset of increasing fatigue and productive cough over a six-month period. On admission to the hospital, physical examination was essentially negative, but the chest roentgenogram showed a mass in the right upper lung field. At bronchoscopy the size of the apical and posterior segmental orifices was reduced, and a bulging of the medial wall of the right main stem bronchus was seen. A scalene fat-pad biopsy was negative. Thoracotomy was performed, and an extensive tumor of the right apex extending to the chest wall was found. Resection was not feasible, so radioactive yttrium was injected into the tumor mass. Two months following surgery a nodule appeared over the upper portion of the left tibia which rapidly increased in size. Roentgenogram of the leg revealed extensive periosteal proliferation of the bones comprising the left knee, with an osteolytic lesion in the proximal shaft of the tibia (Fig. 2). Deep radiation therapy was started over the tibia with some relief of pain, but the patient continued a rapid downhill course and died.

Fig. 1.—The distal phalanges show normal bony structure, with soft-tissue enlargement responsible for the clubbing. Mild periosteal new bone is seen at the distal ends of the radius and ulna.

References 42 and 43.

* References 44 and 45.

Fig. 2.—Periosteal proliferation along the shafts of the bones comprising the left knee. Note the large osteolytic lesion in the proximal shaft of the tibia.

Comment.—An asymptomatic case of periosteal changes associated with an osteolytic lesion of one of the involved bones.

Case 3.—A 37-year-old white man was admitted to the hospital in February, 1954. Three months previously he noticed the sudden onset of pain and swelling in the knees, ankles, toes, and hands. About six weeks later the patient observed that his fingernails were becoming curved, and the finger tips were enlarging. These symptoms grew progressively worse until two weeks prior to admission, when blood-streaked sputum was noted.

Physical examination on admission was essentially negative, except for a temperature of 100.4 F, moderate clubbing of the fingers and toes, and marked swelling of the wrists and ankles. All the joints of both the upper and lower extremities were tender to palpation, and movements were moderately restricted. Roentgenogram of the chest revealed a density in the medial portion of the upper half of the right lung. Films of the extremities showed marked periosteal proliferation of the fingers, the metacarpals, the radii, the ulnae, and the long bones of the lower extremities (Fig. 3). At bronchoscopy, the bronchus of the right upper lobe was retracted. A right pneumonectomy and mediastinal lymph-node dissection were performed even though extensive mediastinal metastases were present. Within one week following surgry, the arthropathic symptoms were markedly relieved, and a decrease in the amount of

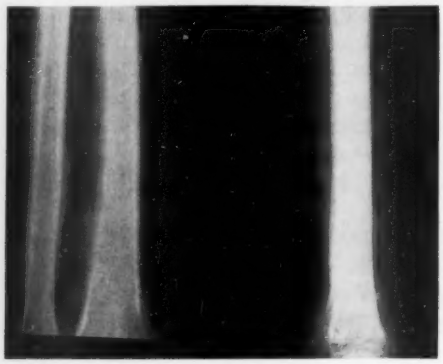

Fig. 3.—Marked irregular periosteal new bone formation is noted along the shafts of the radius and ulna, especially at the distal ends.

clubbing was noted. The pathologic report of the surgical specimen was a squamous-cell bronchogenic carcinoma.

Patient was then allowed to go home but five weeks later was readmitted. A film of the dorsal spine revealed a collapse of the body of the ninth dorsal vertebra due to metastatic involvement. Repeat films of the hands and forearms showed marked decrease in the periosteal changes noted two months previously (Fig. 4). Deep x-ray

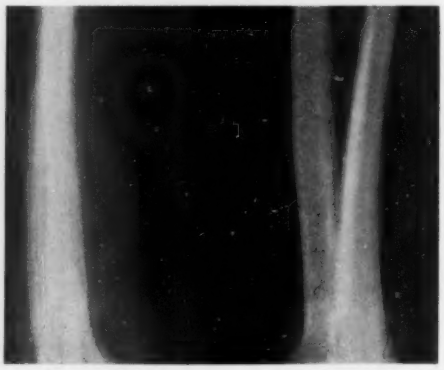

Fig. 4.—Marked decrease in the periosteal changes noted in Figure 3 is seen two months after pneumonectomy.

therapy to the chest was started, but the patient died 10 days later.

Comment.—This case illustrates the symptomatic and roentgenologic improvement following surgical removal of the neoplasm.

Case 4.—A 68-year-old white man was admitted to the hospital with a four-month history of pain and aching in the left elbow and right leg, swelling

of the right knee, productive cough, and 50 lb. weight loss. Physical examination revealed a thin, cachectic, elderly man, moderately dyspneic at rest, with a temperature of 99.4 F. Fine rales were present at both lung bases, and the liver was enlarged 2 fingerbreadths below the right costal margin. The left elbow was swollen and tender, and all movements were restricted. Similarly the right knee exhibited all the signs of an acutely inflamed joint. Marked clubbing of the fingers and toes was present, with cyanosis of the nail beds.

Chest roentgenogram revealed a dense mass extending from the left hilum into the left lower lung field. Two air-fluid levels were noted in the mass, while small scattered nodules were present throughout the right lung. Sputa examinations were positive for atypical cells. X-rays of the long bones showed osteolytic lesions at the medial aspect of the lower end of the left humerus and of the right femur just above the medial condyle. Periosteal new-bone formation was seen at the upper ends of the tibiae and fibulae. Roentgenograms of the hands showed tufting and hypertrophic changes in the distal phalanges and periosteal changes in the middle phalanges and radii (Fig. 5).

Fig. 5.—The distal phalanges show tufting of the distal ends and hypertrophic flaring of the proximal ends. Periosteal proliferation is noted along the shafts of the middle phalanges and the radii.

Palliative radiation therapy to the elbow and knee were given, with a marked decrease in pain resulting. Four weeks after admission, the patient quietly died.

Comment.—In this case of marked clubbing and hypertrophic osteoarthropathy bone changes were present in the distal phalanges.

CASE 5.—A 66-year-old white man was examined by his private physician because of a 10 lb. weight loss over a period of several months. Bronchoscopy revealed a friable lesion in the right main-stem bronchus, which proved to be an oat-cell epidermoid carcinoma. The patient was admitted to the hospital complaining of increasing dyspnea. On physical examination coarse inspiratory and expiratory wheezes were heard over the anterior and posterior right chest. The nail beds were slightly cyanotic, but no clubbing of the fingers was noted. Chest roentgenogram revealed an ill-defined density in the right infrahilar area. A supraclavicular node biopsy contained metastatic anaplastic carcinoma. Three weeks after admission, clubbing suddenly appeared. This persisted until death occurred, five days later.

Comment.—In this case the sudden onset of clubbing occurred late in the course of the bronchogenic carcinoma.

CASE 6.—A 64-year-old white man noted the gradual onset of malaise, generalized weakness, and dyspnea during the summer of 1953. Five months later a troublesome cough productive of bloodstreaked sputum appeared, followed by pain and stiffness of the knees. In July, 1954, he entered the hospital, after all the above symptoms had shown a steady worsening. Physical examination was essentially negative except for slight clubbing of the fingers. Roentgenogram of the chest revealed a 13 cm. dense rounded mass in the left perihilar region extending outwards to the left lateral thoracic wall. Anaplastic carcinoma cells were found in the sputa. At thoracotomy an inoperable undifferentiated squamous-cell carcinoma was found adherent to the chest wall and involving the left upper lobe, lingula, upper portion of the left lower lobe, aorta, and pulmonary vessels. As a palliative measure, 23 mc. of colloidal zirconyl radiophosphate were injected into the major portion of the tumor mass. This was followed by a course of deep x-ray therapy consisting of 2400 r to the chest. Two weeks after discharge from hospital, pain, stiffness, and swelling of the right hand, the knees, and the ankles appeared, associated with a feeling of soreness in the nipples. He was readmitted in January, 1955, at which time the clubbing was more marked, and gynecomastia was present. Roentgenograms showed periosteal proliferation along the shafts of the tibiae, fibulae (Fig. 6), and distal ends of the femora. Intermittent fever with temperature up to 101 F was present, and the pain in the large joints and tenderness of the extremities became increasingly severe. After analgesics and sedation failed to provide relief, daily intravenous injection of corticotropin was begun.

Dramatic improvement resulted within several days. The pain, tenderness, and swelling rapidly subsided, and after one week the patient was free of all bone and joint symptoms. Maintenance

Fig. 6.—Periosteal proliferation along the shafts of the tibia and fibula.

doses of oral hydrocortisone were given, and for the five months preceding his death, the patient remained asymptomatic. A definite decrease in clubbing was noted, and all the joints previously involved were now painless and freely movable, although repeat roentgenograms showed no change in the periosteal proliferation. In July, 1955, following a bout of dyspnea, the patient suddenly died.

Comment.—The unusual features of this case were the gynecomastia and dramatic relief of symptoms by corticotropin (ACTH).

Comment

The constant association of clubbing of the fingers and hypertrophic osteoarthropathy has been known for many years, but only in recent times has it been realized that the two conditions are intimately related. All authorities are agreed that the bone and joint changes represent a further extension of the clubbing process.

Although clubbing may involve one digit, as in cases following local trauma, or may be unilateral, as seen with superior sulcus tumors or aneurysms of the proximal aorta or its branches, by far the commonest variety is a symmetrical enlargement of the ends of the fingers and toes. In this type of clubbing, Lovell [30] described the following constant findings:

1. The normal obtuse angle between the proximal part of the nail and the soft tissue over its root is flattened.

2. The nail bed is more fluctuant than normal.

3. The shape of the nail usually shows an increase in curvature in one or both planes.

4. There is an increase in volume of the distal segment of the finger.

Other signs which may be present include enlargement of the pulp of the fingers, flushing or unusual glossiness of the skin around the nail, and longitudinal striations in a nail which may grow faster than normal.

Among the various terms used to describe the clinical appearance of the abnormal finger ends, "watch glass," "parrot beak," and "drumstick" are frequently mentioned.

Clubbing may occur as a hereditary phenomenon in otherwise healthy young people or as the acquired type, secondary to other diseases. Bronchogenic carcinoma is now regarded as the commonest cause of this syndrome, but many other intrathoracic lesions have been found. Bronchiectasis, empyema, pulmonary tuberculosis, and lung abscess have already been mentioned. Pneumonoconiosis, atelectasis, and chest deformities also constitute a small group. Other chest lesions include lung cysts,[15] intrathoracic fibroma,[49] Hodgkin's disease, carcinoma of the thymus,[50] and pulmonary metastases. Several reports have stressed the high incidence of arthropathy in pleural tumors.†

The remaining causes of clubbing may be divided into the following categories:

1. Cardiac group—clubbing is common in the cyanotic group of congenital heart disease. In subacute bacterial endocarditis, Cotton [54] proved that clubbing was due to emboli in the terminal capillary loops of the fingertips. Rare cases follow chronic congestive failure, especially those due to mitral stenosis.

2. Vascular group—include pulmonary hemangioma or aortic aneurysms acting as mediastinal tumors.

† References 51-53.

3. Hepatic group—clubbing may be seen in hypertrophic or obstructive biliary cirrhosis but is rare in portal cirrhosis.

4. Gastrointestinal group—clubbing has been associated with chronic diarrheal diseases, such as chronic ulcerative colitis, regional enteritis, chronic amebic and bacillary dysentery, intestinal tuberculosis, and the sprue syndrome.

5. Miscellaneous group—includes such conditions as carcinoma of the nasopharynx,[55] myelogenous leukemia,[12] post-thyroidectomy myxedema ‡ and syringomyelia.[58]

The essential pathologic feature of hypertrophic osteoarthropathy consists of a slowly progressive ossifying periostitis, usually found along the distal ends of the shafts of long bones. Most frequently involved are the tibia, fibula, radius, ulna, metacarpals, and metatarsals. In advanced cases, the vertebrae, clavicles, and spines of the scapulae may show changes, but the skull and mandible are never involved. As the periosteum proliferates, new subperiosteal bone is formed which surrounds the original cortex and increases the diameter of the shaft. This pseudocortex is laid down in a thin, irregular layer from 1-5 mm. in thickness, but many layers may be seen, depending upon exacerbations and remissions of the primary disease. Gall and coworkers [59] noted that in the early stage of development the periosteum showed signs of inflammation, thickening, and early division into two layers. The outer or fibrous layer showed a great accumulation of inflammatory cells. The inner cambial layer consisted of a fibrillary intercellular substance which was soon replaced by an osteoid matrix. Shortly after its deposition, the new subperiosteal bone layer fused with the original cortex, and as it became more fully developed and calcified, numerous osteoclasts appeared and caused focal areas of bone resorption. As the resorption continued, a thickened spongy shaft with a rarefying osteitis of the older bone resulted.

The new subperiosteal bone is most marked near the epiphyses and at the points of musculotendinous insertions. It tends to progress to the proximal ends of the bones, but hardly ever are these changes seen in areas covered by the articular capsule. The process is essentially one of hypertrophy, although in extreme cases, the entire structure of the bone may become so atrophic that pathologic fractures result. If the new subperiosteal bone displaces the thickened periosteum rapidly, then pain and tenderness occur, but if the process progresses slowly, the lesion may be asymptomatic. Different portions of the skeleton may show different stages of the disease, advancing rapidly in one area, stationary or regressing elsewhere.

Clubbing is due to a proliferation of all of the soft tissues of the fingertips, but the most marked change is the increase in connective tissue of the nail bed. Dilatation and increase in thickness of the walls of the small blood vessels of the fingertips are also noted. In advanced cases the whole hand may appear enlarged and spade-like. The terminal phalanges may show very little change. Locke [7] described bony proliferation of the distal half of the terminal phalanges in five cases, resulting in a "burr-like" appearance. Several cases have been reported, however, in which complete absorption of the unguinal process occurred.[60]

The joints are involved in at least one-third of the cases, and in some instances the articular symptoms are the most prominent. The articulations adjacent to the affected bones may be enlarged, swollen, and acutely painful and may show an intermittent effusion. The periarticular tissues are affected first, and the most constant abnormality is an edema of the subsynovial tissue, with an accompanying diffuse infiltration of lymphocytes and plasma cells. This chronic synovitis is associated with nonspecific degenerative changes in the articular cartilages. Occasionally pannus may develop and form adhesions across the joint space.

The onset of hypertrophic osteoarthro-

‡ References 56 and 57.

pathy is usually preceded by clubbing of the fingers, although the latter may occur without periosteal proliferation or articular disability. The clubbing may occur gradually and pass unnoticed by the patient, especially in those cases secondary to suppurative chest conditions. In cases secondary to lung tumors, however, the changes in the pulp and nail bed may appear quite suddenly.

In the earlier stages the lesions may be asymptomatic even though roentgen changes are visible. As the condition progresses, aching pains and tenderness are present along the shafts of the long bones. The pain may be severe, aggravated by movement, and may precede the x-ray changes. It may vary in intensity from a mere discomfort to a deep, dull aching which is intermittently present. The skin over the involved areas is warm, reddened, and thickened by a brawny, nonpitting edema. This thickening plus the increased size of the bone are responsible for the heavy, broadened appearance usually seen about the wrists, knees, and ankles. Increased sweating and burning in the skin are noted, and at the same time definite muscular weakness is present.

The involvement is usually symmetrical, and quite often temperatures from 99 to 101 F are observed. The clinical appearance is so similar to rheumatoid arthritis that most authors have described cases in which the patient underwent prolonged treatment for arthritis in spite of a steady progression of symptoms. This confusion is more likely to arise in those cases in which the osteoarthropathy is the first manifestation of an asymptomatic pulmonary condition with normal roentgen findings.

Osteoarthropathy may occur at any age. Kennedy [61] reported clubbing and periosteal proliferation in a 7½-month-old infant with multiple lung abscesses following repeated infections since birth. Similar findings were reported in a 2-year-old infant with chronic pyopneumothorax.[62]

The course of the disease is varied, depending on the activity of the primary condition. All reports have indicated that severe disabling symptoms present for many months may become quiescent within a matter of hours following resection of a lung tumor. However, roentgen changes usually persist for a much longer period. In cases of bronchogenic carcinoma it has been recognized that relief from articular symptoms continues even though surgery has failed to prevent the recurrence of the tumor.

In the early stages of clubbing no changes may be visible on the roentgenogram, but as the process continues an increased flare of the ungual process may be noted. As a result of uneven calcification of the new bone, the periosteum is irregularly raised, and its outline may appear serrated. With exacerbations and remissions of the underlying disease, the new bone may be laid down in thin sheets, producing a tree-trunk layering effect. In the later stages osteoporosis of the cancellous portion and thinning of the original bony cortex may be observed.

The characteristic features of clubbing, arthritic symptoms, and periosteal proliferation especially in the presence of a primary lung condition readily differentiates hypertrophic osteoarthropathy from such conditions as rheumatic fever, rheumatoid arthritis, osteitis deformans, syphilitic periostitis, and acromegaly.

One of the unsolved features of this baffling syndrome is why hypertrophic osteoarthropathy occurs in only 5% of cases of bronchogenic carcinoma. It is agreed that increased peripheral blood flow is an essential factor, but many conditions with altered blood flow through the extremities show no evidence of arthropathy. Therefore, some other factor must be present in this small percentage of cases. Peripheral neoplasms undergoing necrosis, pleural involvement, absorption of toxic products, and decreased arterial saturation have been suggested, but thorough analysis has failed to elicit the common denominator.

In those cases of severe osteoarthropathy where resection of the lung tumor is not possible, the following modalities may be tried:

1. Corticosteroid therapy. In the present series, corticotropin and cortisone were given in one case with excellent symptomatic relief.

2. Vagotomy. Believing that the manifestations of osteoarthropathy were caused by a neural reflex from the lung, Flavell [63] reported five inoperable cases in which immediate relief of symptoms followed vagotomy on the affected side.

3. Phlebotomy. In a severe case of asymptomatic clubbing recently seen by the author, a small nasal hemorrhage resulted in almost complete disappearance of the signs of clubbing. It is possible that the judicious use of phlebotomy may similarly give symptomatic relief by decreasing the peripheral blood flow.

With the ever-increasing incidence of bronchogenic carcinoma, the prompt recognition of the syndrome of osteoarthropathy may result in earlier and more successful treatment in a percentage of cases.

Summary

Six cases of bronchogenic carcinoma exhibiting various clinical manifestations of hypertrophic osteoarthropathy are presented. This syndrome is a chronic proliferative subperiosteal osteitis affecting the distal ends of the extremities. Clubbing of the fingers, swelling, pain, and joint involvement are usually present. A rare idiopathic form has been described, but most cases occur secondary to some underlying pathologic process. Cardiac, hepatic, and intestinal causes have been reported, but suppurative lung conditions and, more recently, bronchogenic carcinoma are now regarded as the commonest cause. This syndrome may appear during the course of a lung cancer, but many cases may be evident long before the lung lesion can be detected.

The earliest stage of osteoarthropathy is manifested by clubbing of the fingers, and all authorities agree that these two processes are intimately related.

Hypertrophic osteoarthropathy occurs in animals, but almost all attempts to reproduce it experimentally have met with failure. An increased peripheral blood flow is present, but some other unknown factor is important in the causation. Decreased arterial saturation, absorption of toxic products, endocrine imbalance, and local anoxia have been suggested, but no experimental evidence has corroborated these theories.

At first the lesion may be asymptomatic, but as the condition progresses, severe bone pain and tenderness are present. Acute joint manifestations are common, and most cases have been wrongly diagnosed as rheumatoid arthritis. Even though the crippling symptoms have been present for long periods, surgical removal or radiation therapy of the lung cancer results in a dramatic amelioration of symptoms.

Although the syndrome of hypertrophic osteoarthropathy occurs in only about 5% of bronchogenic carcinoma, it may provide the clinician with the earliest clue to the detection of pulmonary neoplasms, many times long before the tumor is visible on the roentgenogram. The prompt recognition of this condition can result in earlier diagnosis and more successful treatment of a certain percentage of cases of bronchogenic carcinoma.

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Buckling of the Great Vessels

A Clinical and Angiocardiographic Study

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More than a century ago, Coulson [1] reported the case of an 82-year-old woman "who for some years before her death had a pulsatile tumor, of the size of an orange, just above the right clavicle, in the situation of the carotid. The swelling had not of late increased in size and caused no inconvenience; the woman died from natural decay." This mass, which was considered to be an aneurysm, was shown at postmortem examination to be a tortuous right common carotid artery.

Since then some 117 cases of kinked right common carotid or innominate artery or both have appeared in the literature with thorough reviews by Parkinson [2] and coworkers and Deterling.[3] Buckling of the internal carotid artery, however, appears to have been practically forgotten; Kelly [4] had stressed its benign nature in 1924.

In the present report we wish to call attention to several aspects of buckling not previously mentioned and to reemphasize that buckling is benign. The latter is not always known, in spite of considerable evidence to this effect. In one of the subjects of this study surgical correction of a buckled internal carotid was carried out, and the patient died following surgery.

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Observations

Within the past two years we have studied 16 patients with buckling. There were 13 women and 3 men. The youngest was a woman of 34 with coarctation of the aorta. The other 15 were between 51 and 83 years of age. Hypertension was present in nine; in one, blood pressure record was not available. Eight were obese and heavyset. The manifestations of buckling were pulsating mass at the base of the neck on the right side in six patients, pulsating mass bilaterally in three, pulsating mass confined to the left side of the neck in one, pulsating mass in the suprasternal notch in two; pulsating bulge in the right lateral wall of the posterior pharynx in two (in one there was also a pulsating mass at the base of the right side of the neck), and widened superior mediastinum in two, with one showing calcification of the vessel wall at fluoroscopy. Tables 1 and 2 summarize the findings in our patients. Of particular interest to us were cases 1, 2, 3, 4, 7, and 13.

Report of Cases

CASE 1.—A 52-year-old white man with known hypertension was admitted because of transient right hemiparesis. There was a round large pulsatile mass at the base of the neck on the right side, about 4 cm. in diameter. Its size made us suspect aneurysm rather than buckling. The patient had been aware of it for 15 years, noticing it particularly when he shaved. He did not think that it had changed in size. The angiocardiogram is shown in Figure 1. It demonstrates two buckled vessels side by side, which accounts for the large size of the palpable mass.

CASE 2.—A 63-year-old white woman had asymptomatic hypertension for many years. For several months prior to her admission here she had noted an ill-defined mild soreness in the right side of the throat. Her physician found a pulsatile bulge in the lateral wall of the pharynx and made a presumptive diagnosis of a carotid artery aneurysm. The pulsatile bulge was approximately

TABLE 1.—*Seven Cases of Buckling in Which Angiocardiography Was Done*

Case	Age, Sex	Blood Pressure	Physical Findings	Angiocardiogram, Buckled Vessels	Roentgenogram of Chest	Presenting Condition
1	52,M	270/140	Large pulsating mass right side of neck	Bifurcation of innominate; origin right common carotid	Enlarged left ventricle; widened aorta	Transient right hemiplegia
2	63,F	240/110	Pulsating bulge right side of pharynx; small pulsating mass right side of neck	Right internal carotid; innominate and right common carotid	Enlarged left ventricle; minimal widening of aorta	Ill-defined throat soreness
3	58,F	210/110	Small pulsating mass right side of neck	Innominate just before bifurcation and right common carotid	Minimal enlargement of left ventricle; normal aorta	Routine hypertension clinic visit
4	63,M	210/130	None	Innominate	Enlarged left ventricle; widened aorta	Routine chest film; mediastinal mass
5	52,F	150/100	Small pulsating mass right side of neck	Innominate and right common carotid	Enlarged left ventricle; normal aorta	Routine hypertension clinic visit
6	51,F	200/120	Medium sized pulsating mass right side of neck	Right subclavian	Enlarged left ventricle; minimally uncoiled aorta	Psychosis
7	34,F	210/120, arm; 150/110, leg	Medium sized pulsating mass suprasternal notch	Dilated thyrocervical trunk; bifurcation of dilated innominate	Slight enlargement of left ventricle; widened ascending aorta; small aortic knob; no rib notching	Orthostatic hypotension secondary to sympathectomy

TABLE 2.—*Nine Cases of Buckling—No Angiocardiography*

Case	Age, Sex	Blood Pressure	Physical Findings	Probable Buckled Vessels	Roentgenogram of Chest	Presenting Condition
8	65, F	170/85	Small pulsating mass left side of neck	Left common carotid	Some enlargement of left ventricle; elongated aorta	Arteriosclerosis obliterans
9	83, F	220/120	Medium-sized pulsating neck masses bilaterally	Right and left common carotid; innominate	Enlarged left ventricle; minimal widening of aorta; widened superior mediastinum	Senile psychosis
10	65, F	160/80	Small pulsating neck masses bilaterally	Right and left common carotid	Enlarged left ventricle; widened aorta	Routine cardiac clinic visit
11	60, F	200/112	Medium-sized pulsating neck masses bilaterally	Right and left common carotid	Enlarged left ventricle; moderately widened aorta	Pelvic abscess
12	79, F	*	None	Innominate	Some enlargement of left ventricle; uncoiled aorta; mass right superior mediastinum	Routine chest x-ray
13	73, M	190/85	Pulsating bulge right side of posterior pharynx	Right internal carotid	No chest film	Referred from EENT hospital; no symptoms
14	81, F	130/80	Small pulsating mass right side of neck	Right common carotid	Heart not enlarged; elongated aorta	Routine cardiac clinic visit
15	60, F	150/70	Small pulsating mass right side of neck	Right common carotid	Enlarged left ventricle; widened aorta	Routine cardiac clinic visit
16	75, F	150/70	Small pulsating mass suprasternal notch	? Innominate	Enlarged left ventricle; uncoiled aorta	Routine cardiac clinic visit

* Information not available.

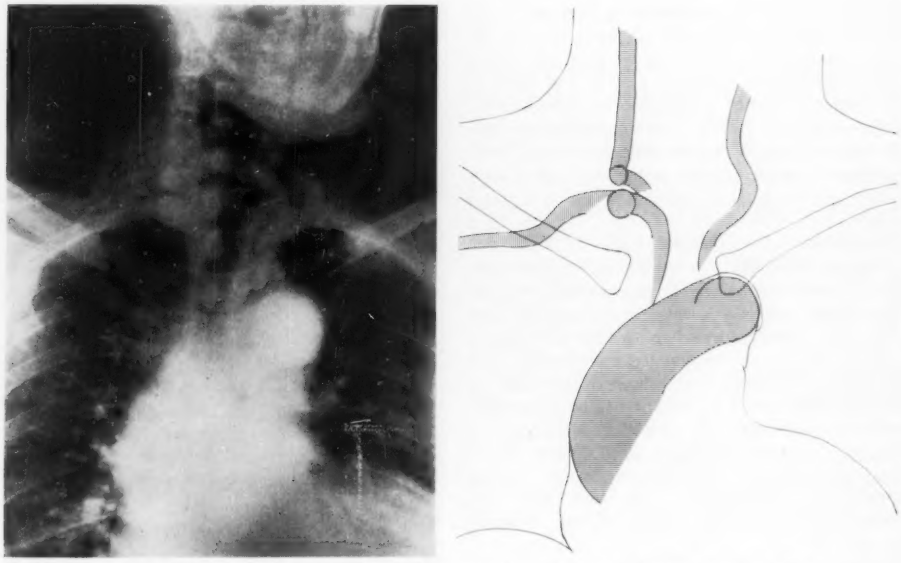

Fig. 1 (Case 1).—Angiocardiogram with accompanying diagram. Anteroposterior view.

1.5 cm. in diameter and was free of tenderness upon palpation. In addition there was a small buckling at the base of the neck on the right side. The patient had not been aware of the latter. The angiocardiogram (Fig. 2) demonstrated a greatly elongated innominate artery displacing the origin

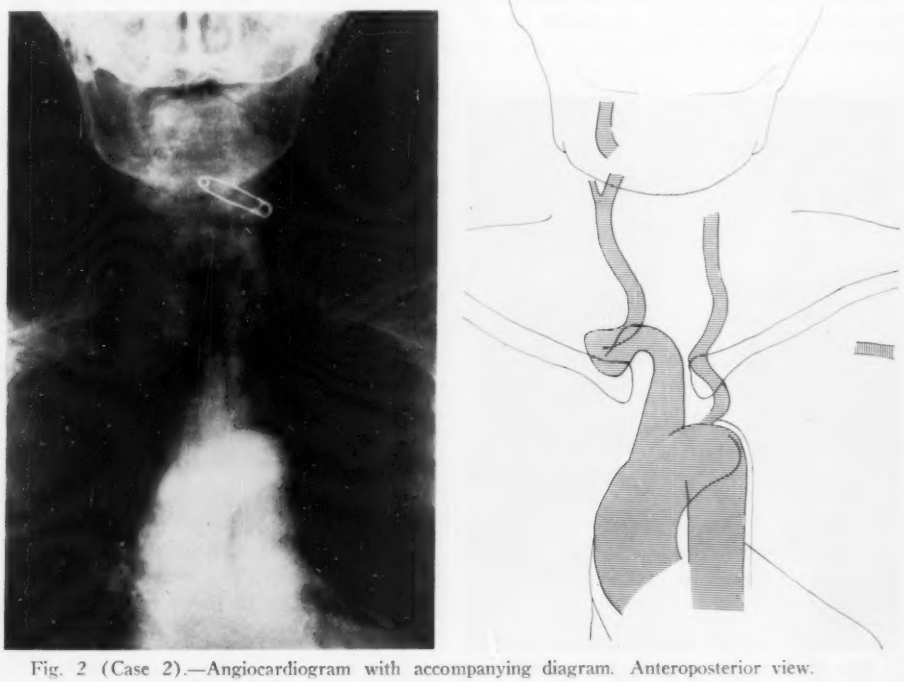

Fig. 2 (Case 2).—Angiocardiogram with accompanying diagram. Anteroposterior view.

of the right common carotid with buckling of the latter. There was deviation of the trachea to the left, the contour at the site of deviation fitting the buckled right common carotid. The mass in the posterior part of the pharynx filled with radiopaque material, but the superimposition of bony structures made delineation difficult. It was interpreted to represent either a tortuous vessel or a small aneurysm. For better visualization direct todopyracet (Diodrast) injection of the right common carotid was suggested but not carried out. Surgical exploration revealed a tortuous and kinked right internal carotid artery, which was resected, the surgeons fearing for its rupture. Left hemiplegia developed, and the patient died several days later, never regaining consciousness. The postmortem examination showed a thrombus in the internal carotid at the site of the suture line, extending distally and completely occluding the lumen. The entire right side of the brain showed marked softening. The buckled right common carotid was inconspicuous and would have been missed by the pathologist had he not been requested to look for it.

CASE 13.—A 72-year-old Negro man was referred from an eye-ear-nose-throat hospital, where he was treated for otitis media and where a pulsating mass in the lateral wall of the right posterior pharynx raised the question of a possible aneurysm of the internal carotid artery. The pulsating mass looked exactly like that described in our Case 2 and in Kelly's[5] illustrations of the buckled right internal carotid.

CASE 7.—A 34-year-old white woman was seen because of severe postural hypotension secondary to a sympathectomy performed at another institution eight years previously. There was no alleviation of her hypertension. The striking thing on inspection was a forcefully pulsating mass in the suprasternal notch, of which the patient had been aware since childhood. This mass could be traced as a dilated vessel extending from the left side of the suprasternal notch to the right and upward, disappearing behind the right sternocleidomastoid. The rest of th physical examination was typical of coarctation of the aorta. The angiocardiogram showed the coarctation to be at the usual site, but the major collateral vessel was interpreted to be a markedly enlarged thyrocervical trunk. Right innominate artery was greatly dilated and buckled at its bifurcation. There was no rib notching, probably because of the route of the collateral circulation. At operation the coarcted segment was resected and an end-to-end anastomosis performed. No large intercostal vessels were encountered. Following surgery the blood pressure fell to normal, and postural hypotension gradually disappeared. The suprasternal pulsation became minimal.

CASE 3.—The interesting feature in this 58-year-old woman with hypertension was that as her elevated blood pressure was brought down to normal by hypotensive drugs, the buckling (Fig. 3) could no longer be seen or felt when she was sitting and could be discerned only with difficulty when she was supine.

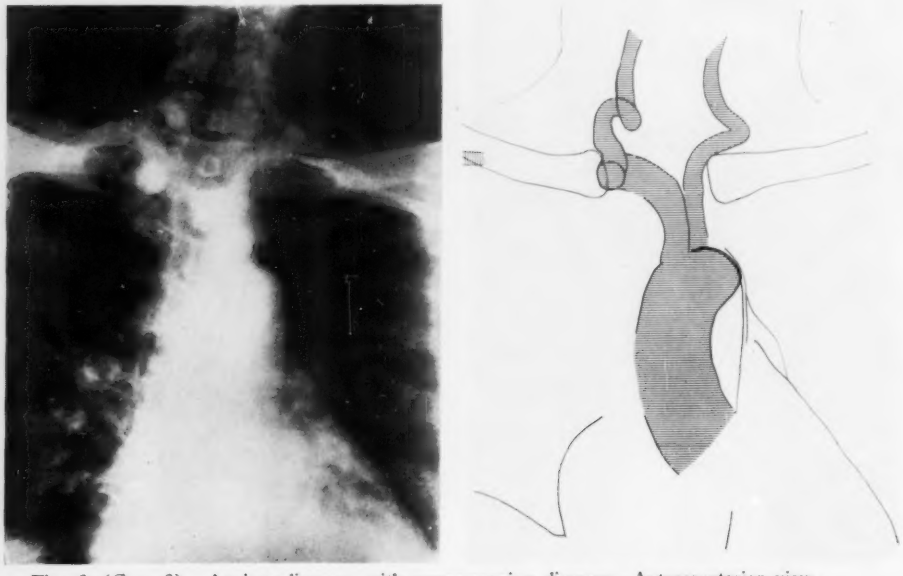

Fig. 3 (Case 3).—Angiocardiogram with accompanying diagram. Anteroposterior view.

CASE 4.—A 63-year-old Negro man with known hypertension had a routine chest roentgenogram which showed a right superior mediastinal mass (Fig. 4). There was no external manifestation of buckling. The angiocardiogram showed this mass to be a widened tortuous innominate artery.

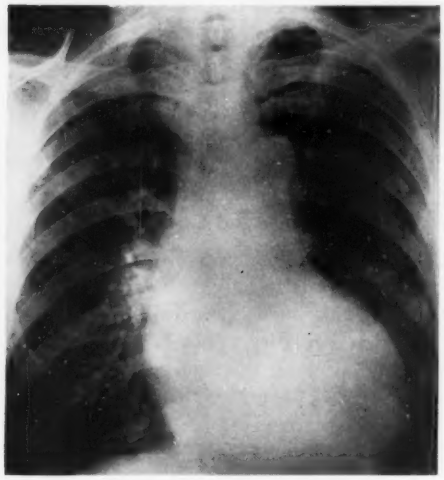

Fig. 4 (Case 4).—Chest roentgenogram. Posteroanterior view.

Comment

As in the first reported case,[1] buckling of the innominate and common carotid arteries is usually seen in women over the age of 50 who are somewhat obese and have hypertension. Typically, there is a pulsatile mass at the base of the neck on the right side, close to the sternocleidomastoid. The mass is usually small, about 2 cm. in diameter, but it may be larger. Buckling may occur in the absence of hypertension. It does appear in men, though much less frequently.* There may be a mediastinal density in the roentgenogram of the chest; this has led to exploratory thoracotomy.[7] The condition has been observed in Negroes † and in Bantus,[9] as well as in Causasians.

Bolotin,[10] in his study of hypertensive patients, has described "left carotid pulsation phenomenon" without a palpable mass. In Parkinson's[2] series of 47 patients there were 2 who in addition to the right-sided buckling had a "similar (though less prominent) pulsatile swelling" on the left side.

Palpable buckling at the base of the neck on the left side without its counterpart on the right was seen in one of our patients. We have encountered one instance of tracheal deviation at the site of a buckled vessel. In one case two buckled vessels side by side felt like a single large mass and were suspected to be an aneurysm. These three aspects of buckling to the best of our knowledge have not been previously reported.

With correction of hypertension, buckling tends to disappear.[3] This was demonstrated by our Case 3.

At a routine postmortem examination a buckled vessel is frequently overlooked[3]; this would have been true in Case 2 of our series.

Buckling is usually due to arteriosclerotic tortuosity and kinking of one or more of the following arteries: innominate, right common carotid, right subclavian, and left common carotid. It is often though not always associated with a widened uncoiled aorta. Kyphosis and scoliosis were frequent in Parkinson's[2] series, but not in the others ‡ or in ours. In younger persons aortic insufficiency and especially coarctation of the aorta must be considered.§

Buckling was studied by angiocardiography in seven of our patients. We found two previous reports on this subject, a retrospective study by Honig and associates || in which 104 angiocardiograms of patients with hypertensive or arteriosclerotic disease were reviewed, revealing 12 cases of "significant buckling of the innominate artery." Four of the twelve showed a pulsating mass at the base of the right side of the neck, and in one case an exploratory thoracotomy was performed for a right superior mediastinal density seen on a conventional roentgenogram. No tumor was found, and postoperative angiocardiogram showed a buckled innominate artery. In

* References 2, 3, 6, and 7.

† References 3 and 8.

‡ References 3, 7, and 9.

§ References 2, 3, 7, and 11.

|| References 7 and 12.

the other report, by Deterling,[3] angiocardiograms were obtained in 8 of 21 patients.

We studied one patient with true aneurysm of the innominate artery. This appears in the angiocardiogram as a distinct circular density immediately above the arch of the aorta—a picture distinct from those of buckling which we have illustrated.

Buckling of the internal carotid artery presents a special problem.¶ It appears as a symptomless pulsating bulge in the lateral part of the pharynx. In 1925, Kelly[5] reported 150 consecutive cases (59 males and 91 females) and reviewed the literature. He divided his cases into two groups: those showing pulsation without a bulge, referred to as "pulsation," and those with a pulsating bulge, which he called "prominent vessel." In the latter group there were 27 patients under 15 years of age, of which 5 were less than 5 years old. Prominent vessels were bilateral in one-third of Kelly's cases. When the condition was unilateral, it was more often on the right. Kelly believed that in the young, tortuosity of the internal carotid is a developmental abnormality, the normal straightening of the artery being incomplete, whereas in the old, it is due to arteriosclerotic widening and dilatation. In Kelly's # series, 22 were over the age of 60 and at least 3 in their 70's. Women predominated; hypertension was not a frequent denominator. Kelly stressed the "unchanging size" of the buckled vessels "over periods of months and years" and stated that "in several cases I have thought that the bulging was slightly bigger than previously, but in no instance has rupture threatened and in no case that I know of has this taken place," in spite of the fact that the affected vessel might show sacculation and thinning of its wall. This is also attested to by others.* In Rowlands and Swan's[14] case there was marked S-shaped tortuosity of both internal carotid arteries, with sacculation and thinning of the wall, yet it was an accidental postmortem finding in a 94-year-old woman.

It is of interest that Portmann and Dupouy[18] quote several reports of what appears to have been a buckled internal carotid being mistaken for a pharyngeal abscess, for which surgical drainage was done with dire outcome. It is surprising that buckling of the internal carotid is not mentioned in a number of ear, nose, and throat textbooks.†

Summary and Conclusions

A review of the literature and the 16 patients in our study show quite clearly that buckling of the great vessels is a benign condition. Surgery is not indicated.

Buckling is a common condition. The frequency of diagnosis depends on the interest of the observer.

The buckled vessels can be demonstrated by angiocardiography and if need be by direct carotid injection and thus differentiated from aneurysm.

Isolated aneurysm of the common carotid near its origin is considered to be rare. When it does occur, it is usually an extension of an innominate aneurysm, which is the basic lesion.‡ Aneurysm of the internal carotid presenting into the pharynx is likewise quite uncommon.§

The clinical features of special interest in the present study were as follows: (*a*) palpable left sided buckling in the absence of its counterpart on the right side; (*b*) tracheal deviation secondary to a buckled vessel; (*c*) two buckled vessels side by side, resulting in a large pulsating mass which suggested an aneurysm; (*d*) two cases of a buckled right internal carotid artery.

Addendum

Since completion of this communication we have seen five additional patients (four women and one man) with buckling of the

¶ References 4 and 13.

References 5 and 13.

* References 14-17.

† References 19-22.

‡ References 2 and 3.

§ References 5 and 23.

right common carotid artery. Four had hypertension. Ages ranged between 48 and 73 years.

Dr. John M. Evans brought to our attention patients to be studied and helped in the preparation of this manuscript. Dr. Elizabeth H. Hill gave permission to use Case 6, which was studied by her at the District of Columbia General Hospital.

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Hypoglycemia in Primary Carcinoma of the Liver

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Introduction

In this journal Nadler and Wolfer,[1] in 1929, first recorded the occurrence of hypoglycemia in a patient with a primary carcinoma of the liver. Since then the association has been reported on six further occasions.* Of these seven reports four have emanated from the United States of America and one each from Belgium, Germany, and Sweden, countries in which the tumor is relatively uncommon. As far as we are aware, hitherto there has been no report of the association from areas where the tumor is possessed of a relatively high incidence.

Two patients with primary carcinoma of the liver associated with hypoglycemia were seen in the course of consulting practice, and the findings in these patients led us to the observations which are the subject of this communication. It will be established that hypoglycemia is not the rarity which the paucity of reports in the literature suggests, and the results of a series of investigations will be presented which shed light on the mechanism of production of the hypoglycemia.

Material and Methods

Twenty-seven consecutive Chinese patients with primary carcinoma of the liver admitted to the University Department of Medicine, Queen Mary Hospital, were investigated. The diagnosis was confirmed by needle biopsy, and necropsy was subsequently performed on all save three patients. Twenty-three were hepatomas of massive type, and the remaining four were cholangiocarcinomas. The findings in the two patients encountered in the course of consulting practice, responsible for focussing our attention on this problem, are included. Both had massive hepatomas. The patients with hepatomas are divided into two groups, Group 1 consisting of 9 patients in which persistent hypoglycemia developed and Group 2, of 16 patients without hypoglycemia.

When the specimen obtained on needle biopsy was adequate, it was divided into two parts, one part being used in the histological study and the other for the estimation of glycogen. This was possible in seven of the patients in Group 1 and five of the patients in Group 2. The technique has previously been reported.* When necropsy was performed within 24 hours of death, specimens were taken from the tumor and from the residual liver and the glycogen content estimated.

In order to eliminate the obvious disadvantages of glucose administered orally the intravenous dextrose tolerance test described by Lozner, Winkler, Taylor, and Peters [9] was used. Following withdrawal of a fasting sample of venous blood, 50 ml. of 50% dextrose was injected intravenously, and specimens of venous blood were taken into fluoride tubes at intervals of 5, 15, 30, 45, 60, 90, and 120 minutes thereafter. From time to time the intravenous dextrose tolerance test developed by Thorn, Koef, Lewis, and Olsen [10] was employed. In this method the dextrose is given intravenously as a 20% solution (0.5 gm. per kilogram) over a period of 30 minutes. For reasons shown later this test was not employed as a routine.

To determine the response to epinephrine, a fasting sample of venous blood was taken, and 1 ml. of 1:1000 epinephrine hydrochloride was injected subcutaneously and the site of injection massaged vigorously. Specimens of venous blood were obtained at intervals of 10, 20, 40, 60, and 90 minutes thereafter.

It should be noted that in Group 1 patients once hypoglycemia had developed rapidly absorbed carbohydrate was not withheld during the night,

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The University Department of Medicine and Queen Mary Hospital; Professor (Dr. McFadzean) and Clinical Assistant (Dr. Yeung).

* References 2-7.

but attempt was made to ensure no intake for four hours before the tests.

Blood sugar was estimated by the method of Folin and Wu[31] as modified by Fiorentino and Giannettasio.[32]

The serum inorganic phosphate was determined by the method of Fiske and Subarrow[33] on specimens obtained during the intravenous dextrose tolerance test.

Glycogen was estimated by the anthrone method described by Morris.[34]

Observations

Certain relevant data in the nine patients with hypoglycemia are set out in Table 1. While symptoms of hypoglycemia are attributed to all save one, Case 3, it should be noted that they were elicited only on direct questioning in four, Cases 2, 4, 7, and 9.

TABLE 1.—*Relevant Data in the Nine Patients with Massive Hepatoma Who Developed Persistent Hypoglycemia*

Case No.	Duration of Subjective Symptoms of Illness Before Onset of Hypoglycemia	Duration of Illness Following Onset of Hypoglycemia	Lowest Blood Sugar Level, Mg./100 Ml.	Symptoms of Hypoglycemia								
				Hunger	Cold Sweats	Weakness	Dizziness	Restlessness	Apprehension	Mental Disturbance	Coma	Convulsions
1	2 mo.	4½ mo.	20	+	+	+	+	+	+	+	+	+
2	3 mo.	10 days	25	+	+	+	+	−	−	−	−	−
3	Unknown	10 days	50	−	−	−	−	−	−	−	−	−
4	5 mo.	6 mo.	37	+	+	+	+	−	−	−	−	−
5	2 mo.	14 days	33	+	+	+	+	−	+	−	+	−
6	5 wk.	25 days	30	+	+	+	+	+	+	+	+	+
7	2 mo.	10 days	51	+	−	+	+	−	−	−	−	−
8	2 mo.	39 days	30	+	+	+	−	−	+	−	+	+
9	1½ mo.	2 mo.	32	+	+	+	+	−	+	−	−	−

Fasting Blood Sugar

Group 1.—Case 4, who survived for six months following the onset of hypoglycemia, was observed only for the first three months of this period during which hypoglycemia persisted. With the exception of Case 1 hypoglycemic levels persisted in all of the remaining cases to the time of death.

In Case 1 during the first six weeks following admission to hospital the fasting blood sugar ranged from 69 to 81 mg. per 100 ml. Hypoglycemia then developed and persisted for seven weeks. At the end of this time the patient complained of severe pain in the tumor, which rapidly increased in size and subsequently softened. In this phase he lapsed into semicoma, which was unaffected by the administration of dextrose. Upon recovery the fasting blood sugar was found to be within normal limits, and it so remained for the succeeding four weeks, when hypoglycemia again developed and persisted until death, two weeks later. At necropsy the massive primary tumor in the right lobe of the liver showed very extensive necrosis, and one large and many small metastases were present in the left lobe.

Group 2.—The duration of observation in this group of 16 patients with primary hepatoma without hypoglycemia ranged from 2 to 17 weeks, the average being 5½ weeks. The fasting blood sugar was estimated at intervals not greater than seven days. The mean values in each case ranged from 72 to 109 mg. per 100 ml., the aver-

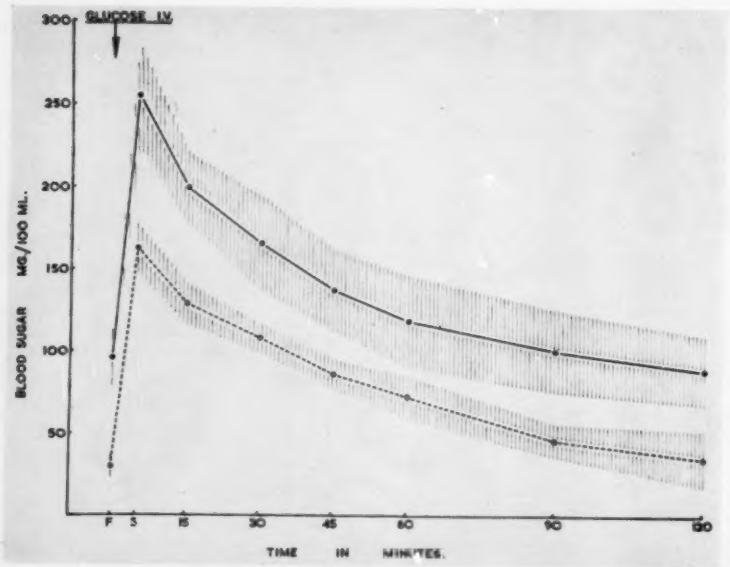

Fig. 1. — The results of the intravenous dextrose tolerance tests in the 9 patients in Group 1 (interrupted line), contrasted with those in 14 healthy controls (continuous line). The results are expressed as the mean plus or minus one standard deviation.

age being 84 mg. per 100 ml. In five cases the fasting level fell below 70 mg. per 100 ml. (four being between 60 and 70 and one being 40 mg. per 100 ml.), but in no case did these lower levels persist.

Intravenous Dextrose Tolerance

The results, expressed as the mean plus or minus one standard deviation, of the intravenous dextrose tolerance tests in the 9 patients in Group 1 once hypoglycemia had developed are set out in Figure 1, and those in the 16 patients in Group 2 are shown similarly expressed in Figure 2. In each group the results are contrasted with the findings in 14 healthy controls. It will be seen that the rate of disappearance of dextrose from the peripheral blood in each

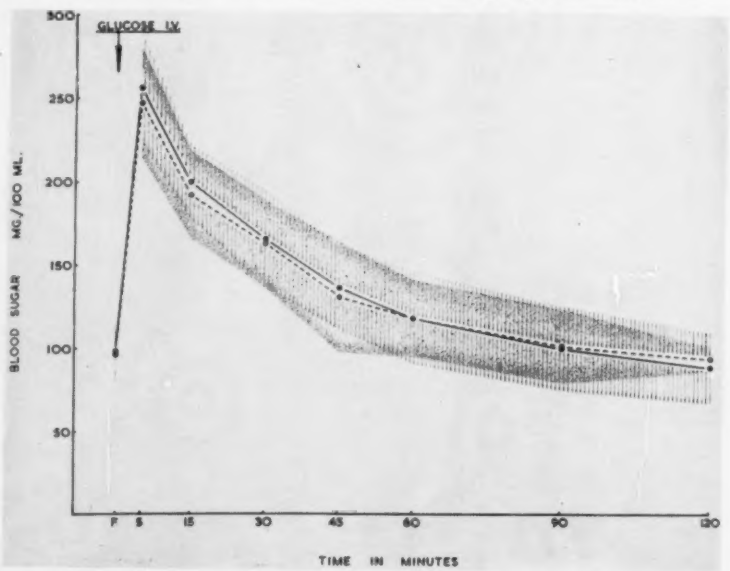

Fig. 2. — The results of the intravenous dextrose tolerance tests in 16 patients in Group 2 (interrupted line), contrasted with those in 14 healthy controls (continuous line). The results are expressed as the mean plus or minus one standard deviation.

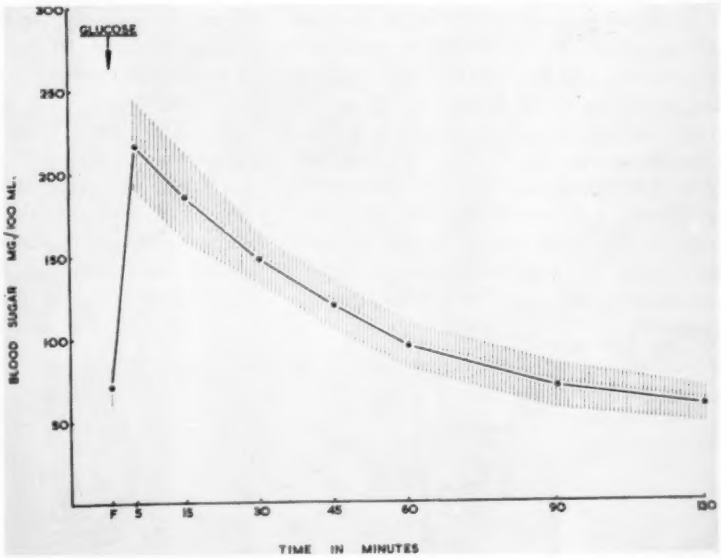

Fig. 3. — The results of 14 intravenous dextrose tolerance tests performed on one patient, Case 1. The results are expressed as the mean plus or minus one standard deviation.

group does not differ significantly from that in the normal controls.

In six patients (three in Group 1 and three in Group 2) the test was carried out on one occasion only, and in eight (one in Group 1 and seven in Group 2) it was repeated once. In the remaining 11 (5 in Group 1 and 6 in Group 2) the test was performed at intervals on from 3 to 14 occasions, the average being 6. In none of those patients in which the test was repeated was there significant change in the rate of disappearance of dextrose from the peripheral blood; the curve remained essentially unchanged. Given in Figure 3 as a typical example is the mean plus or minus one standard deviation in each of 14 tests performed at intervals over a period of four months in one patient, Case 1. It will be seen that the standard deviation is small.

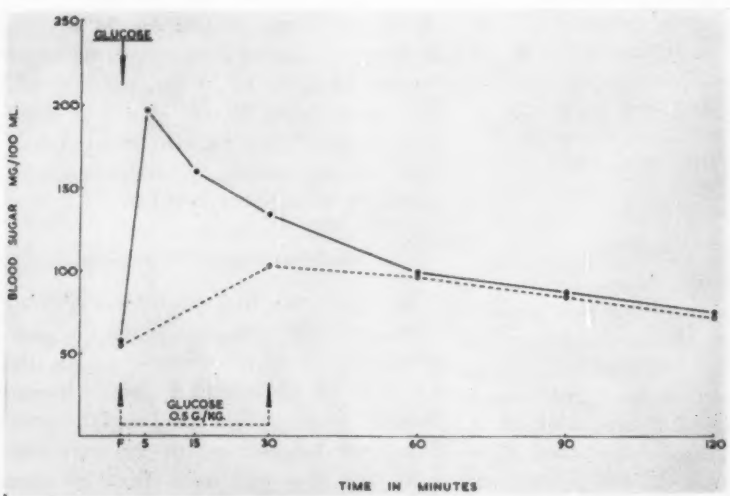

Fig. 4. — The results of the intravenous dextrose tolerance test of Thorn and co-workers[10] (interrupted line), contrasted with those of the test of Lozner and co-workers.[9] (continuous line). The tests were performed on the same patient, Case 8, on consecutive days.

An example of the results of the dextrose tolerance test of Thorn and co-workers [10] is compared with those of the test of Lozner and co-workers [9] in Figure 4. These two tests were performed on the same patient, Case 8, on consecutive days. The absence of hyperglycemia in the former test is to be noted, and, since it was considered possible that such absence might of itself lead to failure to influence serum inorganic phosphorus, this test was not routinely employed.

100 ml., respectively. In the remaining case an initial rise of 18 mg. occurred, but at 60 minutes there was a fall to 15 mg. below the fasting level. Case 8 is of special interest. The patient when first seen was in hypoglycemia coma and over a period of four hours was given 350 gm. of dextrose. One hour later the blood sugar was 48 mg. per 100 ml. Epinephrine was given, and the blood sugar fell to 38 mg. per 100 ml. A biopsy of the tumor was done at this time, and the yield of glycogen was

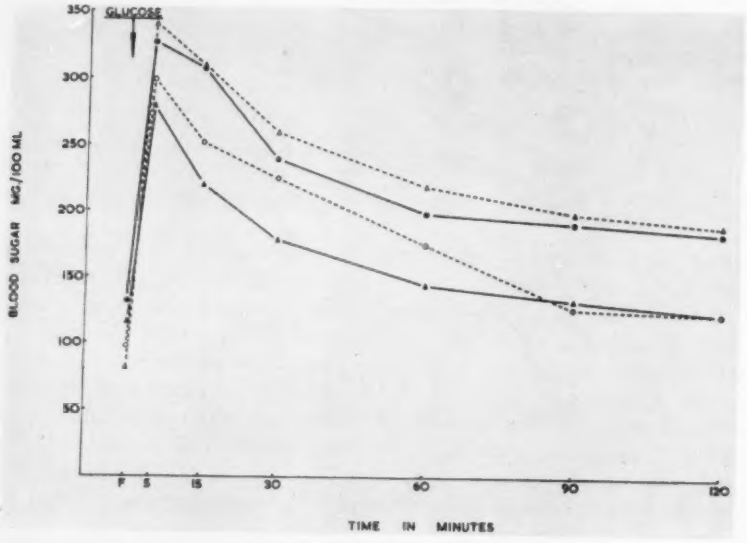

Fig. 5. — The results of the intravenous dextrose tolerance test in the four patients with cholangiocarcinoma.

Given in Figure 5 are the results of the intravenous dextrose tolerance test in the four patients with cholangiocarcinoma. It will be seen that the blood sugar level in each case at 120 minutes is significantly higher than the fasting level, which in two was abnormally high.

Epinephrine Test

The results of the epinephrine test in Groups 1 and 2 are depicted in Figures 6 and 7, respectively. In each case the results are contrasted with those obtained in eight healthy controls. In Group 1 there was a fall in blood sugar in two cases, three showed no significant change, and three showed a rise of 18, 22, and 30 mg. per 100 ml. Group 2 showed a rise in blood sugar ranging from 18 to 54 mg. per 100 ml., the average being 31 mg. It will be noted from Figure 7 that the rise occurred later than in the controls, a phenomenon for which we have no explanation.

Serum Inorganic Phosphorus

In the absence of hypoglycemia no constant pattern of change in serum inorganic phosphorus was encountered during the course of the intravenous dextrose tolerance tests in Group 1 and 2. The fall varied from case to case and in the same case from time to time, ranging from less than

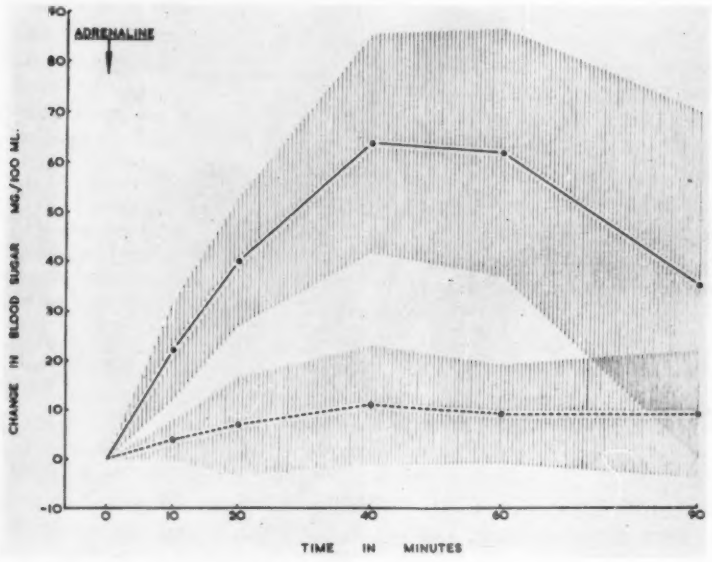

Fig. 6. — The results of epinephrine test in the nine patients in Group 1 (interrupted line), contrasted with those in eight healthy controls (continuous line). The results are expressed as the mean plus or minus one standard deviation.

10% to between 20% and 30%. The pattern of response was constant once hypoglycemia had developed, and in no case with hypoglycemia did the serum inorganic phosphorus fall by more than 10%. Figure 8, in which is depicted the findings in Case 9, illustrates the responses encountered.

Glycogen Content

In Table 2 are given the results of the estimations of glycogen in both the biopsy and necropsy material in Groups 1 and 2. In all four cases of cholangiocarcinoma no glycogen was found in either the biopsy or necropsy specimens of the tumors.

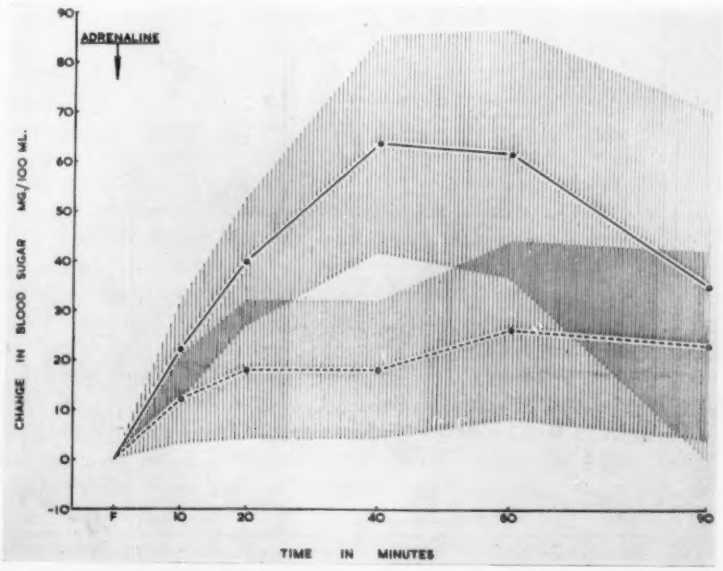

Fig. 7. — The results of the epinephrine test in the 16 patients in Group 2 (interrupted line), contrasted with those in 8 healthy controls (continuous line). The results are expressed as the mean plus or minus one standard deviation.

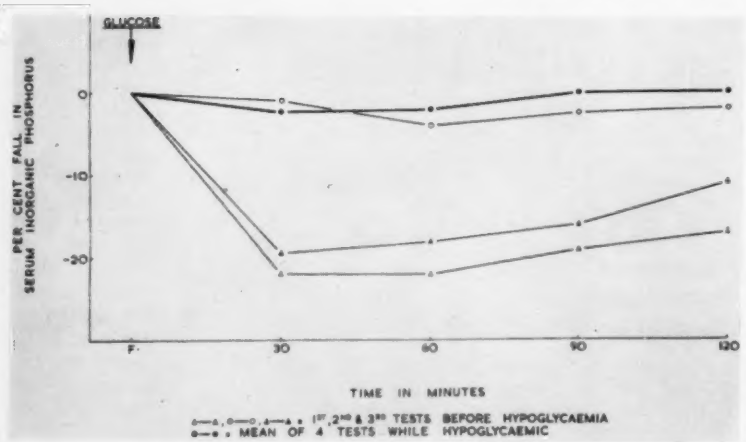

Fig. 8. — The fall in serum inorganic phosphorus, expressed as percentages of the fasting levels encountered during seven intravenous dextrose tolerance tests in the same patient, Case 9.

Effect of Cortisone

Three of the patients with hypoglycemia, Cases 3, 5, and 6, were given cortisone, 200 mg. daily in four divided doses. The fasting blood sugar was raised in two cases from 40 and 54 mg. per 100 ml. to 75 and 81 mg. per 100 ml., respectively, after 48 hours. Withdrawal of the cortisone re-

TABLE 2.—*The Glycogen Content of Specimens Obtained by Needle Biopsy and/or at Necropsy in Eighteen Cases of Massive Hepatoma* *

Group	Case No.	Blood Sugar at Time of Biopsy, Mg./100 Ml.	Glycogen Content of Tumor Biopsy, Mg./Gm.	Necropsy			Differentiation of Tumor
				Glycogen Content, Mg./Gm.		Time after Death, Hr.	
				Tumor	Residual Liver		
1	1	69	8	1.5	1.5	7	Well-differentiated
	2	44	6	5.2	1.3	18	Anaplastic
	3	--	--	0.8	1.0	16	Anaplastic
	4	63	13	--	--		Well-differentiated
	5	60	5	1.1	1.6	14	Anaplastic
	6	51	9	1.3	1.0	20	Anaplastic
	7	50	7	--	--	--	Anaplastic
	8	40	30	--	--	--	Well-differentiated
2	10	--	--	33.0	16.0	12	Well-differentiated
	11	82	12	--	--	--	Well-differentiated
	12	80	6	6.6	1.8	15	Well-differentiated
	13	76	13	--	--	--	Well-differentiated
	14	--	--	0	0	12	Anaplastic
	15	88	16	2.0	1.0	20	Well-differentiated
	16	--	--	1.4	1.0	22	Anaplastic
	17	--	--	0.5	0.8	22	Well-differentiated
	18	78	5	2.5	1.5	24	Anaplastic
	19	--	--	1.8	1.2	20	Anaplastic
	20	--	--	0.8	0	10	Well-differentiated

* Case 8 was given 350 gm. of dextrose intravenously in the 5 hours before biopsy, and Case 10, 450 gm. in the 12 hours before death.

sulted in a return to hypoglycemic levels. The fasting level in the remaining case was unaffected.

Comment

In the series of 23 consecutive cases of hepatoma, hypoglycemia occurred in 7 (30%). The singular absence of reports from areas in which this tumor is relatively common can only be explained by oversight. While many of the symptoms given in Table 1 might well be overlooked, the development of hunger in a patient with carcinoma of the liver especially when death is not far off, is so bizarre as to suggest the diagnosis. Hypoglycemia was not encountered in four consecutive cases of cholangiocarcinoma.

Conn and Seltzer,[15] in an excellent review of idiopathic hypoglycemia, considered that one of the criteria in the diagnosis of hepatogenic hypoglycemia was a plateau dextrose tolerance test. Since such was not encountered in any of the our cases of hypoglycemia, it would seem that two fundamentally distinct mechanisms resulting in hypoglycemia are to be encountered in hepatic disease.

It is held that if liver disease interferes at all with the dextrose tolerance test a plateau curve results. For example, Forsham and Thorn,[16] employing an intravenous dextrose tolerance test in a variety of liver diseases, found the fasting level to be slightly above normal, but the significant finding was the blood sugar after two hours, which was far above the fasting level. This again was not encountered in any of the cases of hepatoma even when the test was repeated at intervals embracing a period in which there had developed the grossest evidence of impaired liver function. In contrast, in cholangiocarcinoma a plateau curve developed relatively early in the disease when evidence of impairment of liver function was minimal. It may be concluded that the dextrose tolerance curve in hepatoma fundamentally differs from that encountered in other liver diseases, including cholangiocarcinoma.

Glycogenesis in the liver and peripheral utilization account for the removal of dextrose administered intravenously. Pollack, Millet, Essex, Mann, and Bollman[17] perfused the isolated hind leg of the dog with dextrose and showed that a brisk fall in serum inorganic phosphorus occurred, whereas no such fall was encountered on perfusion of the isolated liver. These results were confirmed by Soskin, Levine, and Hechter,[18] and the fall in serum inorganic phosphorus following the intravenous administration of dextrose has become accepted as a valid criterion for peripheral utilization. Forsham and Thorn[16] found in their cases of liver disease, in which a plateau dextrose tolerance curve had developed, that during the test there was a prompt and sustained fall in inorganic phosphorus averaging 37%. They concluded that the behavior of serum inorganic phosphorus during the intravenous dextrose tolerance test was so consistent as to afford a simple means of differentiating between peripheral underutilization of dextrose in diabetes and decreased liver glycogen storage capacity in liver disease. In contrast to these results the response of the serum inorganic phosphorus in the cases of hepatoma in the absence of hypoglycemia varied widely from case to case and in the same case. Commonly no significant fall was encountered. In the hypoglycemic group once hypoglycemia had developed the response was constant and was in all cases less than 10%. If the validity of a fall in serum inorganic phosphorus as a criterion of peripheral utilization of dextrose be accepted, then it must be concluded that, when such fall was absent, the dextrose administered was being diverted away from peripheral utilization, and it can only be assumed that it was being taken up by the liver. This assumption is supported by the report by Forsham and Thorn[16] of a series of cases with normal sugar curves associated with a fall in inorganic serum phosphorus significantly less than the accepted normal. The one feature common to all their cases appeared to be depleted liver

glycogen. They concluded that the depleted glycogen reserve was being replenished rapidly by the administered dextrose, which was thus diverted away from peripheral utilization.

We find it inconceivable that the residual liver tissue progressively encroached upon by the tumor should retain unimpaired an ability to cope with dextrose comparable to that of the normal organ. Indeed, if the results of the Thorn and co-workers'[10] modification of the intravenous dextrose tolerance test be considered, the uptake by the liver in which hepatoma has developed is greater than that reported by Forsham and Thorn[16] for intact livers with depleted glycogen reserves. It must be concluded that the tumor is responsible in whole or in part for this uptake.

As a result of the diversion of exogenous dextrose to the tumor the glycogen reserves in the residual liver are reduced or nonexistent. We submit that the results of the epinephrine test and of the gloycogen estimations at necropsy support this conclusion. In the fasting state these reserves are rapidly exhausted, the demand for dextrose by the tumor continues unabated and can only be met by gluconeogenesis. The natural progress of the disease is a progressive increase in demand and coincident reduction in supply. The constancy of the results of the intravenous dextrose tolerance test is such that we wonder not at the occurrence of hypoglycemia in hepatoma but that it is not present in all. This concept affords explanation of the findings in Case 1. The onset of massive necrosis in the tumor reduced demand below supply, and the hypoglycemia was corrected. Demand once again outstripped supply with growth of the metastases in the contralateral lobe.

The quantity of dextrose taken up by the tumor varies widely. In the present series the maximum carbohydrate intake per day required in any patient to prevent hypoglycemia developing was 825 gm. The patient reported by Nadler and Wolfer[1] required a daily intake of 872 gm., that reported by Beers and Morton,[3] 1210 gm., and Crawford's case,[2] 1700 to 2200 gm. If these figures afford indication of the consumption of dextrose by the tumor, which together with the body needs must be met largely by gluconeogenesis, then herein lies in part at least explanation for the rapid wasting encountered in this disease.

Orr and Stickland,[19] from observations on the carcinoma of the liver induced in rats by the prolonged administration of *p*-dimethylaminoazobenzene, concluded that in the transition to malignancy there occurred abruptly a complete change in the type of metabolism in the liver cells in that the sole substrate used for glycolysis changed from glycogen to glucose. Olson,[20] employing C^{14}-labelled carbohydrate intermediates in observations on the same tumor, also concluded that as the liver undergoes neoplasia the metabolism of carbohydrate is altered so that dextrose entering the cell is diverted almost entirely from the metabolic pathway leading to glycogen formation to that resulting in lactic acid formation. Hou and McFadzean,[8] however, showed that hepatomas in Chinese may contain substantial quantities of glycogen and concluded that the extent of diversion of "metabolic traffic" from the pathway leading to glycogen synthesis to that resulting in lactic acid formation varied and is not almost complete as suggested by Orr and Stickland[19] and by Olson.[20] They found that the variation in diversion appeared to be inversely related to the degree of differentiation of the tumor, being greater in the anaplastic and less in the well differentiated. Their findings are confirmed in the present series. Since the highest content of glycogen was found in two cases to which large quantities of dextrose had been given prior to obtaining the specimen, the possibility arises that the glycogen content may be influenced by the dextrose intake.

It is assumed that the glycogen is available to the tumor as a source of dextrose but the existence of significant quantities of glycogen in the tumor in the presence of hypoglycemic levels in the peripheral blood suggests that this source is not avail-

able to the body economy. The finding in Case 8 of a concentration of 30 mg. per gram of glycogen in the presence of hypoglycemia one hour after the administration of epinephrine strongly supports this view. Material obtained by biopsy, however, cannot be taken to represent the glycogen content of the tumor as a whole. Unlike cholangiocarcinoma the histological picture in hepatoma may vary in different sections from the same tumor, some areas presenting appearances suggestive of cholangiocarcinoma. Indeed, such differing appearances may be encountered in the same section. Further, Hou and McFadzean [8] have shown that even in well-differentiated hepatomas the glycogen content of different areas in the same tumor may vary widely. The glycogen content of the tumor was estimated in only two of the previously recorded cases, both on specimens obtained at necropsy performed an unknown time after death. None was found in the case reported by Nadler and Wolfer,[1] but in Engel's case [4] the yield was 43 mg. per 100 gm. The former case was in hypoglycemic coma for two and one-half hours before death.

McFadzean and Todd,[21] from an extensive study of the intrahepatic circulation in hepatoma, concluded that the venous drainage of the highly vascular tumor is provided by branches from the portal vein. Only when these branches become obstructed by infiltration did the hepatic vein enter into the venous drainage of the tumor. They considered that when the primary tumor was massive the greater part of the blood reaching the contralateral lobe by the portal vein came from the circulation within the tumor. It is manifest that such a circulation might well influence the function of the residual liver cells and have a part to play in the development of hypoglycemia, but nevertheless we submit that the functional disturbance essentially remains the outcome of demand for dextrose outstripping supply.

There would be no problem in the management of hypoglycemia in primary carcinoma of the liver if coma developed in all and persisted to death. Unfortunately, distressing hypoglycemic symptoms may develop relatively early in the course of the disease. Under such circumstances the repeated administration of dextrose is, for obvious reasons, far from satisfactory, and we believe that cortisone may well have a place in the management of the hypoglycemia.

It should be noted that hypoglycemia has been reported on six occasions in association with tumors other than that of the pancreas and of the liver.† Silvis and Simon [26] pointed out that the common denominator of all the reported cases was a large tumor with displacement of the viscera. Since no investigation comparable to those reported here was undertaken, it would be idle to speculate as to the mechanism of hypoglycemia in these cases.

Summary and Conclusions

Twenty-seven consecutive and two additional patients with primary carcinoma of the liver have been investigated. Twenty-five had massive hepatomas and four, cholangiocarcinomas. Persistent hypoglycemia was encountered in 9 of the patients with hepatoma, 7 being in the consecutive series of 23 (30%). Hypoglycemia in primary carcinoma of the liver is therefore far from being the rarity which the paucity of reports in the literature suggests.

In none of the patients with hypoglycemia did the intravenous dextrose tolerance test give a plateau curve. It is concluded that the hypoglycemia is fundamentally distinct from that reported in other diseases of the liver.

The rate of disappearance of dextrose injected intravenously in each of the patients with hepatoma was not significantly different from that encountered in healthy controls even when the test was repeated at intervals throughout the course of the disease, including periods in which liver function was grossly deranged. In contrast, in each of the four patients with cholangio-

† References 22-26.

carcinoma, relatively early in the disease a plateau curve developed. It is concluded that the intravenous dextrose tolerance test yields fundamentally different results in hepatoma from those encountered in other diseases of the liver, including cholangiocarcinoma.

The fall in serum inorganic phosphorus during the intravenous dextrose tolerance test in the absence of hypoglycemia varied from case to case and in the same case from time to time. Commonly the fall was significantly less than that encountered in the normal. Following the onset of hypoglycemia, however, the response was constant in each case, and in all it was less than 10%. In the absence of a significant fall in serum inorganic phosphorus, it is concluded that the dextrose is being diverted away from peripheral utilization and that the tumor must be responsible in whole or part for the diversion. This diversion of dextrose results in depletion of the glycogen reserves in the residual liver, and evidence is presented to this effect. The demand for dextrose by the tumor persists in the fasting state; such reserves of glycogen as are present in the residual liver are rapidly exhausted, and the demand is met by gluconeogenesis. The natural progress of the disease is toward progressive increase in demand with coincident reduction in supply. Once demand exceeds supply, hypoglycemia results.

Previous observations, indicating that in hepatoma in Chinese the extent of diversion of glucose metabolism from the pathway leading to glycogen synthesis varies, are confirmed. The demonstration of significant quantities of glycogen within the hepatoma in the presence of hypoglycemic levels in the peripheral blood suggests that the glycogen within the tumor is not available to the body economy.

The administration of cortisone raised the fasting blood sugar to within normal limits in two of three patients with hypoglycemia, and it is concluded that cortisone may have a place in the management of such cases.

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The Diagnosis of Boeck's Sarcoid by Skeletal Muscle Biopsy

Report of Four Cases

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Skeletal muscle biopsy has been found useful in obtaining pathological tissue representative of the underlying disease process in a number of conditions. These include trichiniasis and polyarteritis nodosa,[2] in which specimens of diagnostic value may be found. In addition, in dermatomyositis [3] and certain types of muscular dystrophy helpful histological evidence may be found by such a biopsy.[4] In 1952, Myers [5] and his co-workers, reporting on the joint and skeletal manifestations of sarcoidosis, noted granulomata in the skeletal muscle of three of their cases. They suggested that random gastrocnemius muscle biopsy be further evaluated as a diagnostic procedure in Boeck's sarcoid. Since then one report has appeared in the foreign literature dealing with muscle biopsy in the diagnosis of sarcoidosis.[6] In view of the importance of obtaining a specimen of tissue containing the characteristic granuloma as a diagnostic aid in the patient suspected of this disease, further study of the possibilities of skeletal muscle biopsy was undertaken. The following is a report of the results of random gastrocnemius muscle biopsy performed in five cases of sarcoidosis. Material containing granuloma consistent with Boeck's disease was found in four of the five cases. In two patients biopsy of skeletal muscle was done in conjunction with biopsy of another site (skin and lymph node), which also gave pathological material consistent with sarcoid. In two additional patients muscle biopsy provided the only positive histologic evidence, as there were no skin lesions, enlarged lymph nodes, or other areas suitable for biopsy. In another patient no pathologic material was found in the muscle, although evidence of lung lesions was present, and biopsy of a lymph node in the supraclavicular area contained granulomata of sarcoid.

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Report of Cases

CASE 1.—This 39-year-old white man entered for evaluation of his pulmonary status. He had been a patient in a local sanitorium one year previously, following an episode of hemoptysis. Sputum studies there were said to have been negative for acid-fast bacilli. He was discharged after five months' stay. Chronic cough continued.

Physical Examination.—There was increase in the anteroposterior diameter of the chest. A few scattered inspiratory rales were present in the upper lung fields bilaterally. There were no peripheral lymphadenopathy, hepatosplenomegaly, or eye or skin lesions.

Laboratory Data.—Hemogram and urine were normal. The total serum protein was 7.9 gm. per 100 cc.; serum albumin, 4.3 gm. per 100 cc.; globulin, 3.0 gm. per 100 cc.; serum calcium, 10.2 mg. per 100 cc. Smear and culture of the sputum for tubercle bacilli were negative.

X-ray of the chest showed infiltrative densities scattered in both lung fields. No cavitation was noted. Hilar areas and cardiac shadow were normal.

Course.—First- and second-strength tuberculin skin tests were negative (PPD.). In view of lack of confirmatory evidence to support a diagnosis of tuberculosis, and with the evidence of suggestion

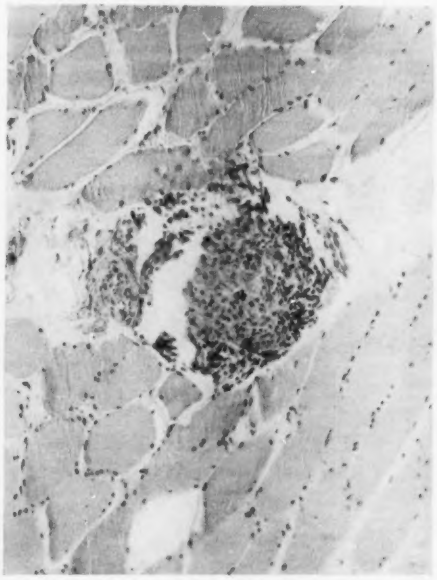

Fig. 1.—Skeletal muscle biopsy in sarcoidosis. Case 1, section from random gastrocnemius muscle specimen. Sarcoid granuloma present.

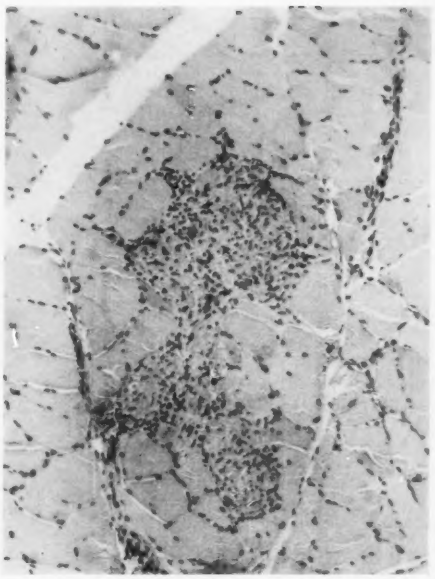

Fig. 2.—Skeletal muscle biopsy in sarcoidosis. Case 2, section from random gastrocnemius muscle specimen. Sarcoid lesions present.

of increased serum globulin, a diagnosis of sarcoidosis was entertained as the explanation of the pulmonary densities. A random gastrocnemius biopsy was carried out which disclosed a granuloma of muscle consistent with Boeck's sarcoid (Fig. 1).

CASE 2.—This 25-year-old white man was referred for evaluation of the finding of bilateral pulmonary infiltrations discovered in a routine chest x-ray survey. No history of industrial dust exposure could be elicited. Study at another hospital, including bronchoscopy and sputum examinations for acid-fast organisms, failed to disclose positive diagnostic evidence of the underlying disease process.

Physical examination was within normal limits.

Laboratory Data.—Hemogram, urinalysis, and serum albumin and globulin were normal. Sputum studies for tuberculosis were negative.

X-ray of the chest showed a diffuse granulation throughout both lung fields. The heart and mediastinum were within normal limits.

Course.—Tuberculin skin tests were negative in first and second strength (PPD.). A positive diagnosis could not be made, but sarcoidosis was suspected. Random gastrocnemius biopsy was carried out, as no peripheral nodes or skin lesions were available for biopsy. Sections of the muscle disclosed granulomata consistent with Boeck's sarcoid (Fig. 2).

CASE 3.—This 44-year-old man entered for repair of bilateral inguinal hernias. He complained, in addition, of chronic cough and wheeze.

Physical examination showed, in addition to bilateral inguinal hernias, the liver to be enlarged 4 cm. below the costal margin in the midclavicular line, and the spleen was palpable in the left upper abdomen. There were several small nodes noted in the right supraclavicular area.

Laboratory Data.—Hemogram and urine were normal. Serum albumin was 4.9 gm. per 100 cc., and serum globulin, 2.1 gm. per 100 cc. Serum bilirubin was 1.9 mg. per 100 cc.; thymold turbidity, 5 units, and serology, negative.

X-rays of the chest showed markedly enlarged paratracheal and hilar lymph nodes. The lung fields and heart shadow were normal. Films of the hands were normal.

Course.—The patient underwent a biopsy of a right supraclavicular node and also a random gastrocnemius muscle biopsy. In both the lymph node and muscle were found granulomata consistent with sarcoidosis (fig. 3).

CASE 4.—This 28-year-old white man had been considered possibly to have sarcoidosis in a previous admission two years before, although a tissue specimen consistent with that diagnosis had not been obtained. The positive findings then were primarily limited to a diffuse stippling of the lung fields in a chest x-ray, without hilar node enlargement. This was interpreted as consistent with

Fig. 3.—Skeletal muscle biopsy in sarcoidosis. Case 3, section from random gastrocnemius muscle specimen. Sarcoid lesion present.

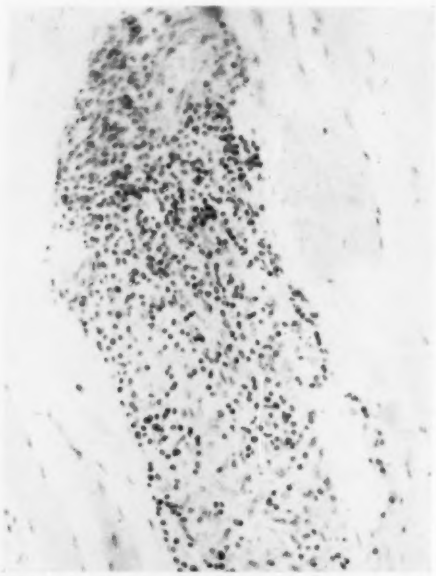

Fig. 4.—Skeletal muscle biopsy in sarcoidosis. Case 4, section from random gastrocnemius muscle specimen. Sarcoid granuloma present.

sarcoidosis or pneumoconiosis. He was readmitted with anorexia and weight loss.

Physical examination showed several small supraclavicular lymph nodes, small erythematous papules, and plaques located on the forearm and trunk; otherwise the findings were within normal limits.

Laboratory Data.—Hemogram, serology, and blood sugar were normal. Serum albumin was 3.7 gm. per 100 cc., and serum globulin, 2.5 gm. per 100 cc. Urine showed 1+ albumin, one to three red blood cells, and two to four white blood cells in the sediment.

X-ray of the chest showed increased densities scattered in the peripheral lung fields and enlarged hilar nodes.

Course.—The patient underwent biopsy of a skin lesion and also random gastrocnemius muscle biopsy. Both biopsy sites contained granulomata consistent with sarcoidosis (Fig. 4).

CASE 5.—This 23-year-old man entered the hospital because of 16 lb. weight loss and abnormal densities in the chest x-ray.

Physical examination was within the normal limits.

Laboratory Data.—Hemogram and urine were normal. Serum calcium and phosphorus were normal. Serum albumin was 4.4 gm. per 100 cc., and globulin, 1.8 gm. per 100 cc.

Chest x-ray widening of the hilar shadows bilaterally. The lung fields and heart shadows were normal. X-rays of both hands were normal.

Course.—First- and second-strength tuberculin skin tests were negative. The patient was suspected of having sarcoidosis. Results of a random gastrocnemius muscle biopsy were negative, showing normal skeletal muscle. A left supraclavicular exploration disclosed a small node overlying the scalene muscle. This was removed, and sections disclosed granuloma consistent with sarcoidosis.

Comment

The advantage of skeletal muscle biopsy as a diagnostic procedure in this disease is twofold. Firstly, the technique of the procedure is simple and safe and can be carried out under local anesthesia. As a technical procedure it would rate above lymph node, liver, or lung biopsy, three other sites of biopsy in sarcoidosis. The skin is another simple biopsy site, provided lesions are present for excision, but these do not occur in all patients. Secondly, the diagnostic specificity of finding a granuloma consistent with sarcoid in muscle appears somewhat greater than finding such a lesion in the liver or a lymph node. This depends on the fact that the granuloma seen in sarcoid is not pathognomonic of that entity, but

may occur in other granulomatous diseases.[7] The lesion may be indistinguishable pathologically from hard tubercles, which may occur without caseation necrosis in certain cases of tuberculosis. However, while tuberculous dissemination not infrequently involves the liver or lymph nodes, its presence in skeletal muscle is a rarity.[8] Other diseases, such as tularemia or brucellosis, may again produce lesions similar to that of sarcoidosis,[7] but muscle invasion is not reported as characteristic.

The crucial point in evaluation of random skeletal-muscle biopsy in sarcoidosis would seem to be the frequency of granulomatous involvement of that tissue site. If such were a rare occurrence, the low incidence of "positive" biopsies would make the procedure unprofitable. Review of the literature to determine the number of instances of skeletal-muscle involvement found by biopsy during life or at autopsy was done by Powell[9] and reveals a total of 24 cases. While this figure might indicate a low incidence of skeletal-muscle granuloma in sarcoidosis, there is reason to believe that it might not be representative of the true incidence. In reports based on autopsy statistics in regard to organ involvement in sarcoid, skeletal muscle is not often mentioned as containing pathological material.[7] However, it should be remembered that skeletal-muscle examination is not a routine at autopsy in many hospitals. Unless specific complaints or lesions were noted during life in respect to the skeletal system, muscle sections are not often examined. Similarly, in regard to biopsy during life, the majority were done because of local muscle symptoms, including pain, atrophy, or nodular masses located in the muscles. Biopsy was done on a variety of muscles, including the supraspinatus, quadriceps femoris, gastrocnemius, and biceps, which were the site of local clinical findings.[9] While a relatively small total number of cases of sarcoidosis with histologically demonstrated muscle granulomata has been documented, nevertheless experience with random muscle biopsy suggests a high incidence of skeletal-muscle involvement. In a study by Maurice,[6] sarcoid granulomata in skeletal muscle were found in five of seven autopsy specimens and in three of six cases on which biopsy was done during life. As noted in our series presented herein, a positive result of muscle biopsy was found in four of five cases. The fact that Boeck's sarcoid tends to be disseminated and widespread also tends support to this possibility. Until routine biopsy of skeletal muscle is done in a large number of persons with sarcoidosis, an accurate incidence of skeletal muscle involvement can not be stated.

Summary and Conclusions

Random skeletal muscle biopsy as a diagnostic measure was carried out in five cases of sarcoidosis. None of the patients had local findings referable to the muscle prior to the biopsy. In four of the five cases, material containing granulomata consistent with sarcoid was obtained.

The literature in regard to skeletal muscle involvement in Boeck's sarcoid is reviewed. Reasons why the incidence of involvement may be higher than so far reported are pointed out. It is suggested that further biopsy studies of skeletal muscle are needed before the true incidence of granuloma in muscle in this disease will be known.

Skeletal muscle biopsy would appear to warrant further use as a diagnostic measure, especially in the patient suspected of Boeck's sarcoid without skin lesions or involved peripheral lymph nodes.

Dr. Herman A. Lawson, Chief, Medical Service, Veterans Administration Hospital, reviewed this paper and gave suggestions in its preparation. Mrs. Rebecca Rinaldi typed the manuscript.

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Tuberculous Pericarditis

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The white cold virgin snow upon my heart
Abates the ardour of my liver. THE TEMPEST, Act 4, Scene I.

The heart is deceitful above all things, and desperately wicked. JEREMIAH, 17:9.

Sir William Gull, on demonstrating tuberculous pericarditis to a physician who had missed the diagnosis, concluded his remarks with "Never mind; if you had detected it, you might have treated it."[1] Times have changed; the detection of this disease is not met with quite the same sense of frustration. However, despite an expanding diagnostic and therapeutic arsenal which has modified the outlook, this remains a serious and not uncommon condition.

The natural history of tuberculosis of the pericardium, treated or untreated, may follow two pathways. This is well illustrated by two cases recently seen at the New England Center Hospital.

Report of Cases

CASE 1.—A 69-year-old white man was admitted on Oct. 25, 1954, with a four-day history of increasing weakness, exertional and paroxysmal nocturnal dyspnea, and some ankle edema. A chest film taken prior to admission had shown increased transcardiac diameter. There was no history of chest pain, tachypnea, fever, sweating, or orthopnea. In the past a right-upper-lobe coin lesion and a history of exposure to lime dust had raised the question of pneumoconiosis.

He was poorly developed and poorly nourished, elderly, and in slight respiratory distress. Temperature was 98 F, pulse 90, respirations 20, and blood pressure 120/90. The neck veins were distended, pulsating, and filled from below. The apical impulse could not be palpated, and the heart tones were distant. Cardiac dullness was percussible to the left anterior axillary line. Pulsus paradoxus was present. Over the right lower lobe posteriorly an area of dullness, decreased resonance, and decreased breath sounds was noted. The liver was felt 3 fingerbreadths below the right costal margin. There was 2+ pitting pretibial and ankle edema and questionable early clubbing of the fingers. Venous pressure was 290 mm. Chest film showed a large pericardial effusion, minimal pulmonary congestion, and small effusion at the right costophrenic angle. Hemogram: RBC 4,000,000; WBC 12,250, with normal differential; hematocrit 45. The urine was negative. Sedimentation rate was 26 mm/1 hour. Low-voltage complexes were recorded in all electrocardiographic leads, with T-wave inversions in Leads I and V_{5-6} and upright T-aV_R.

Course.—On Oct. 27, through a subxiphoid approach, 1000 cc. of serosanguinous fluid was removed from the pericardial sac. The venous pressure fell to 200 mm., and the left border of cardiac dullness receded several centimeters. A pericardial rub appeared above the tap site. The neck veins filled from above, but pulsus paradoxus remained, and arterial pressure was unchanged. Chest films confirmed marked reduction in transcardiac distance. The pericardial fluid contained 1150 RBC and 1100 WBC per cubic millimeter (P., 55%; L., 45%); specific gravity was 1.018; it was submitted for guinea pig inoculation and culture for acid-fast bacilli. The patient was given digitalis and diuretics, and on Nov. 4 treatment was begun with 300 mg. of isoniazid (INH); 12 gm. of aminosalicylic acid (PAS), and 1 gm. of streptomycin daily (the latter changed on Nov. 8 to 0.5 gm. of streptomycin and 0.5 gm. of dihydrostreptomycin). On Nov. 14 his temperature rose to 101.8 F, venous pressure, to 225 mm., and chest film showed increased pericardial fluid. On Nov. 16, 350 cc., and on Nov. 19, 600 cc. of serous fluid was removed, but on Nov. 20 venous pressure was 215 mm., and four days later, 235 mm., at which time 400 cc. of turbid, orange-yellow fluid was drawn and 100 cc. of air injected intrapericardially. X-ray showed hydropneumopericardium with a thick (up to 1 cm.), shaggy wall; the underlying heart had a normal transverse diameter of 13.5 cm.; transthoracic diameter was 30.5 cm. The venous pressure fell only to 225 mm; it rose

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steadily thereafter to 320 mm. on Dec. 2, falling to 255 mm. the next day. Symptoms and signs of congestive failure persisted, and it was believed that the patient had developed the syndrome of constriction. On Dec. 6 he was transferred to the surgical service, and two days later he had a pericardiectomy. Postoperatively the venous pressure fell to 200 mm. He did well subjectively and objectively but developed thrombophlebitis and died suddenly on Dec. 20, probably of a pulmonary embolus.

On Dec. 8 autopsy of guinea pig injected with fluid from the initial pericardicentesis revealed tuberculosis. Two days later this fluid yielded colonies of acid-fast bacilli. On Jan. 3, 1955, guinea pig inoculated from tap fluid of Nov. 19 was found to have tuberculosis. Sputum cultures and inoculations were never positive.

The course data of Case 1 are summarized in Figure 1.

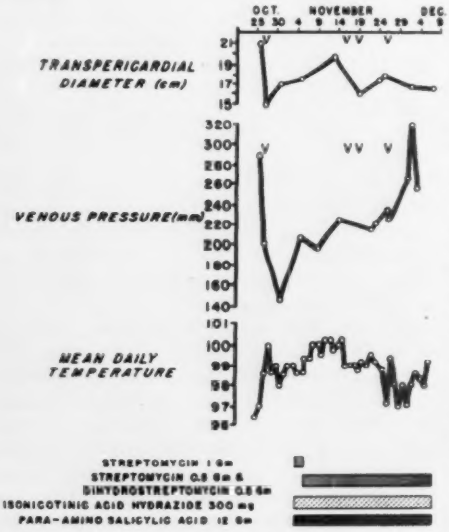

Fig. 1 (Case 1).—Venous pressure continues to rise and pericardial size remains abnormal despite pericardicenteses (indicated by V) and chemotherapy. The last venous pressure reading is probably due to technical error.

Case 2.—First Admission: A 33-year-old white man was paraplegic for 21 years because of collapsed tuberculous vertebrae. He was well until four weeks prior to admission, when he developed intermittent bilateral shoulder and neck pain, worse on inspiration. Two and one-half weeks later he was suddenly awakened by excruciating bilateral shoulder pain plus sharp pain across the mid-anterior chest, both markedly increased on inspiration, and accompanied by marked tachypnea. His temperature was 102 F; he took eight tablets of acetylsalicylic acid, with dulling of pain in one hour. Following this episode pain persisted with some decrease in intensity and became localized to the lower substernal and left parasternal areas, where it was sharp and intermittent, and also to the posterior neck, where it was burning and constant. In both locations exacerbation occurred on inspiration and when lying on the left side. For five days he had had a persistent cough productive of small quantities of colorless, viscid sputum. During this period, oral temperatures varied up to 103 F.

There was no history of known pulmonary tuberculosis or of hemoptysis. A chest film, taken Aug. 10, 1955 (13 days prior to admission) had been read as negative. Systemic review revealed only the paraplegia (including cord bladder) and a recently treated urinary infection. He had had multiple tenotomies for contractures of the lower extremities.

On admission Aug. 23, he was a well developed, flushed white man, appearing chronically and acutely ill, in moderate respiratory distress and sitting up, bending over a pillow for relief of chest pain. Temperature was 102 F; pulse, 112; respirations (mostly diaphragmatic), 32/minute; arterial blood pressure, 110/60. There was marked lordotic and scoliotic deformity of the thoracolumbar spine. The lower extremities were in flaccid paraplegia with marked atrophy, total anesthesia below the seventh dorsal segment, and extensor plantar reflexes. Scattered crepitant and subcrepitant rales over the posterior lung fields and a pleural friction rub in the upper anterior right chest were audible. A loud pericardial rub was present everywhere over the precordium, best heard at the base.

Course.—On Aug. 24 the venous pressure was 180 mm.; there was no pulsus paradoxus. X-ray showed an enlarged, globular heart shadow caused presumably by pericardial effusion. On Aug. 25 350 cc. of viscous, bloody fluid was removed and 100 cc. of air injected intrapericardially, revealing, on x-ray, a shaggy, markedly thickened pericardium and residual fluid with a frothy "head." Coincidentally, the patient felt markedly improved despite a transient temperature rise to 102 F following the procedure. Immediately 1 gm. of streptomycin and 12 gm. of PAS daily were given. On Aug. 29, 300 mg. of INH daily was added. Nine days later (Sept. 7) he was almost asymptomatic, and chest film showed markedly diminished pericardial shadow. On Sept. 9 streptomycin was omitted, to be "held in reserve." Between Sept. 10 and 13 he had a fever with temperature peaks averaging 102 F daily; this was coincident with a subcutaneous abscess over the left hip, from which a coagulase-positive Staphylococcus aureus was cultured and successfully treated with 200 mg. of erythromycin q. i. d. (On Sept. 12 streptomycin had been given again, but was discontinued on

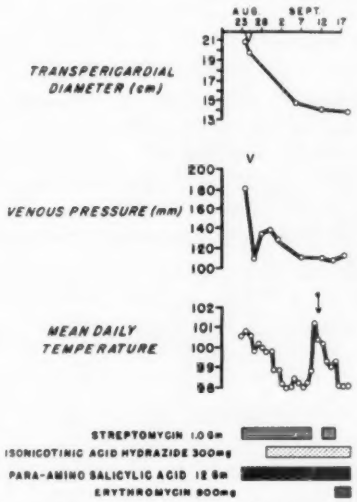

Fig. 2 (Case 2, First Admission).—After a single pericardicentesis (indicated by V), venous pressure and pericardial size progressively decrease to normal. The symbol * indicates aspiration of cutaneous staphylococcal abscess, the apparent cause of the temperature spike.

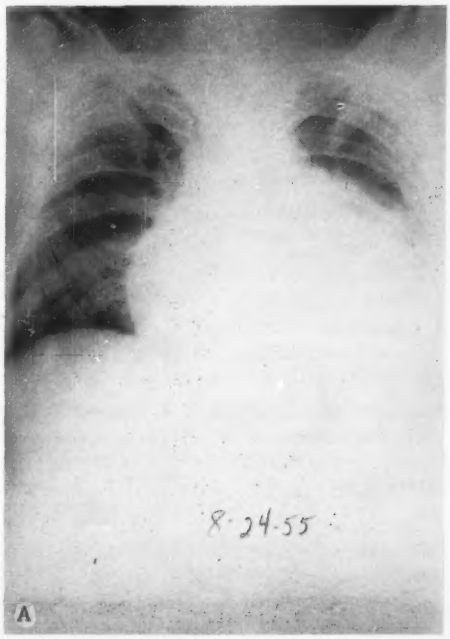

Fig. 3B.—X-ray in Case 2. Aug. 25. Post-air-injection film showing pneumohydropericardium.

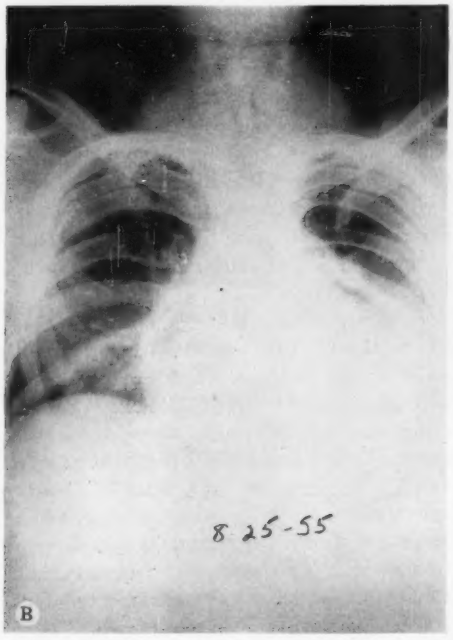

Fig. 3A.—X-ray in Case 2. Aug. 24. Large pericardial effusion. Transpericardial measurement, 20.9 cm.

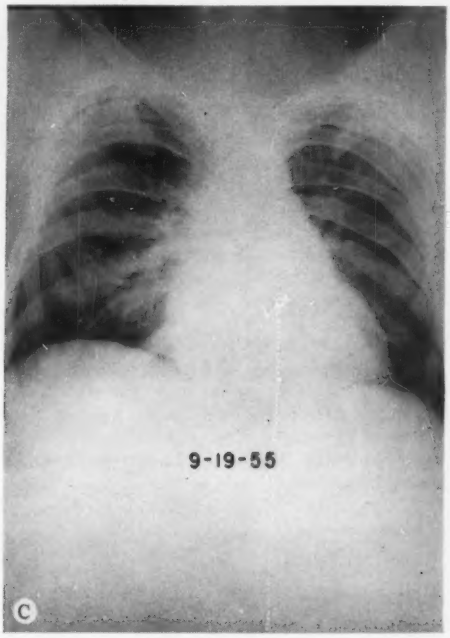

Fig. 3C.—X-ray in Case 2. Sept. 19. Complete resolution of effusion. Transpericardial measurement, 13.8 cm.

Significantly Opposite Characteristics of Cases 1 and 2

	Preceding Tuberculosis of Vertebrae	
	Case 1	Case 2
Onset	Gradual	Sudden and acute
Pain	Absent	Present
Fever	Absent	Present
Cough	Absent	Present
Paroxysmal dyspnea	Absent	Present
Edema	Present	Absent
Increased venous pressure	Persistent, despite pericardicentesis and chemotherapy	Transient (absent following pericardicentesis)
Effusion	Massive and persistent despite therapy	Large, relieved after single tap
Presence of organisms	Demonstrated	Not demonstrated
Ultimate course	Progressive constriction and tamponade	Rapid resolution without detectable residua; acute recurrence with rapid improvement

Sept. 14 without relapse.) He was discharged Sept. 19 (28th hospital day) to a convalescent home. Two to three months' rest on gradually increasing activity, 100 mg. of INH t. i. d., 3 gm. of PAS q. i. d., and symptomatic treatment were recommended.

The course data of Case 2 (first admission) are summarized in Figure 2.

Second Admission: The patient did well until Oct. 28, when all of his presenting complaints returned within a 24-hour period. This time there was no relief from sitting up and leaning forward. He was readmitted Nov. 1, acutely ill and tachypneic but alert and cooperative. Temperature was 99.6 F. There was tachycardia (104/minute), but no rubs or murmurs on admission; the lungs were clear, and there was no venous distention. Venous pressure was 120 mm.; WBC, 12,250, with shift to the left; E. S. R. 21 mm/1 hour; red blood cell count, hemoglobin, and urine, normal. Chest film disclosed an increase in transpericardial diameter to 17.8 cm. Electrocardiogram, while improved considerably over the previous reading (Sept. 19), showed persistence of T-wave inversion in Leads III and VI and diphasic T waves in aV_F and V_{2-4}.

He made satisfactory progress on continuation of INH and PAS therapy plus readministration of streptomycin, at first daily and finally 1.0 gm. twice weekly. Streptomycin was temporarily omitted during a transient maculopapular eruption and eosinophilia. He was afebrile within four days of admission, the highest temperature having been 101.8 F, on Nov. 3. X-ray showed regression of pericardial size to 13.5 cm. by Jan. 3. Lung fields were always clear. Electrocardiograms continued to be consistent with subsiding pericarditis. A rub had been heard on Nov. 2, but was absent after Nov. 12. He was discharged on Jan. 15 (76th hospital day).

The onset, course, and outcome in each of these patients were quite different in several important respects. Both represent instances of the same disease process. Both were actively treated with identical agents. The Table summarizes their distinctly opposite features. These will be shown to be of great prognostic import in this disease.

Comment

Time has added little to the fundamental conclusions of the earliest investigators of pericardial tuberculosis. Rokitansky[2] first described it (1852) and declared from the outset its association with and dependence on an earlier tuberculous lesion.[3] Osler (1893)[1] reported 17 cases and reviewed 1000 consecutive autopsies, of which 275 had tuberculosis, including 7 with tuberculous pericarditis. He concluded that caseous mediastinal nodes were the usual focus for pericardial involvement. Intrapericardial air injection was introduced by Wenckebach, in 1910.*

Incidence.—Since the original recognition of this disease there has been wide disagreement on the incidence of tuberculous pericarditis among even contemporaneous observers. It has been thought "infrequent,"[6] "not common,"[7] and "relatively rare,"[8] as well as "not rare,"[4] "fairly common"[9] and "of greater incidence than suspected."† This last citation would seem to be a fair statement, at least partly because this lesion is a commoner finding for the pathologist than for the clinician.[12]

* References 4 and 5.

† References 10 and 11.

Omitting conditions such as myocardial infarction and uremia, it has been held the commonest type of pericarditis seen in general hospitals (in contrast to "nonspecific pericarditis," considered by the same authors commonest in general practice).[13] Moreover, cases thought to be idiopathic or rheumatic may well be tuberculous,‡ and there is general agreement that it represents at least 7% of all cases of acute pericarditis.§ Furthermore, in large autopsy series,‖ it has been found in up to 1% (certainly a significant figure) and in between 2.5% and 7.8% of all cases of tuberculosis. Interestingly, tuberculous infection has been incriminated as a cause of the rare cholesterol, or "gold paint," pericarditis.¶

Sex and Age.—This is overwhelmingly a disease of males (70%-85%)# and of greater frequency among Negroes,* though the magnitude of the latter (in most series over 50%) varies somewhat with demographic factors. Reports from the southern United States[3] and from Africa[22] are naturally weighted in this respect. All ages are affected,† with the majority in the United States over 40.‡ By contrast, English patients average 21.[19]

Pathogenesis.—It is firmly established that tuberculous pericarditis does not occur as a primary lesion.§ However, it is often the sole manifestation or first overt clinical sign of tuberculosis,‖ for which circumstance the term "clinically primary" tuberculous pericarditis has been coined.¶ Miliary seeding may occur, and, rarely, hematogenous spread from pulmonary, skeletal or genitourinary lesions,# but the important route is by direct extension from caseous mediastinal or hilar nodes.* Failure to demonstrate these nodes by x-ray does not exclude tuberculous infection within them.[10]

Most observers describe the natural history of tuberculous pericarditis in three phases: acute (fibrinous), effusive, and adhesive (constrictive)†; Peel[10] defines an absorptive phase between effusion and constriction. The four-phase schema accords well with the sequence of events in "typical" cases not arrested before chronicity. Nevertheless, it must be emphasized that progression may not occur according to plan even in the absence of treatment, and one or more phases may go unrecognized or appear to be lacking. While effusion is almost invariable,[8] the initial (acute, fibrinous) phase is quite often not observed,‡ and the disease may pass insidiously to constriction. Indeed, it has been held that in chronic constrictive pericarditis, absence of a history of the acute phase is the rule.[19]

Symptoms.—The patient's complaints are most often the least striking manifestation of acute tuberculous pericarditis (unlike Case 2). Chambliss[27] found 31 of 61 patients with chronic cardiac compression in whom there was no history of an acute phase. Children may be at play with serious acute tuberculous pericarditis[11] and adults at work for a long time with a massive effusion.§ Andrews[19] reports a Marine in active training with an enormous amount of tuberculous pericardial fluid discovered on routine x-ray. On the other hand, unusual patients may present a striking picture of discomfort, such as the case observed by Janovsky and co-workers.[14] This man was seen during numerous 48-hour episodes of severe anginal pain with ECG changes typical of pericarditis, each spontaneously regressing. After five years of sometimes monthly recurrence, effusion

‡ References 4, 9, 12, and 14.
§ References 9, 13, and 15.
‖ References 1, 2, and 16.
¶ References 17 and 18.
# References 3, 8, 12, 19, and 20.
* References 3, 13, and 21.
† References 13, 15, 19, and 21.
‡ References 6, 13, and 15.
§ References 3, 4, 8, 13, and 23.
‖ References 12 and 13.
¶ References 3, 14, 21, and 23.
# References 8, 13, and 24.

* References 1, 3, 4, 8, 13, and 25.
† References 4, 13, 22, and 26.
‡ References 10, 11, and 13.
§ References 4 and 12.

accompanied an attack, and acid-fast organisms were cultured from the fluid.

In Wood's collection of 41 cases, onset was gradual in 28, sudden in 9, and asymptomatic in 4.[8] This preponderance of insidious development is concurred in by other investigators.‖ Sudden onset (of definite prognostic import) is commoner in younger persons and in Caucasians.[8] Constitutional symptoms—fever, malaise, anorexia—are usually minimal in the absence of tamponade.¶ Dyspnea is the commonest presenting complaint # and is usually mild, except in some cases of massive effusion.[4] Pain, when present, may be substernal, like angina, or in the neck, either shoulder or arm, epigastrium or interscapular region; sharp, dull, gripping, aching, and constricting varieties are described.* It is aggravated by inspiration if the neighboring pleura is involved,[9] and in some cases adjacent pleuritis represents the sole source of pain production.[29] The occurrence of cough (caused by pressure on trachea and bronchi) is even more capricious, regarded by some as "frequent"[4] and by others insignificant.† Patients first seen in early tamponade are more likely to have constitutional symptoms (Case 1), dyspnea, and cough, as well as hoarseness, dysphagia, hiccup, abdominal pain, and peripheral edema.‡

Signs.—In those cases seen before the development of effusion, the objective findings are those of any pericarditis sicca; friction rub is often heard and felt.§ The ECG is almost always abnormal, with changes explained by subpericardial myocarditis, viz., tachycardia; low voltage; RST segment elevations, frequently with an upward concavity and without reciprocal depressions; tall, peaked, or dome-shaped T waves. These changes persist variably, regardless of clinical remission (Case 2), with late return of the RST to the isoelectric line, after which the T waves may become inverted.‖ In tuberculous pericarditis, arrhythmias have been reported in as many as 10% to 26% of large series. These included atrial fibrillation and flutter, extrasystoles, and all degrees of heart block. The blocks occurred either without digitalis or with subdigitalizing doses.¶ Phasic respiratory changes in the QRS form and duration are common.[3]

Effusion is the rule.# Large to massive effusions (300 to 3500 cc. or more) are comparatively common and most characteristic of this type of pericarditis.* In a Bantu patient the area of cardiac dullness extended from axilla to axilla.[22] The sac has been known to distend to the posterior chest wall, where it has been readily tapped.[35] Rapidity of fluid accumulation is the key factor in cardiac embarrassment. The slow production of even 2 liters is often well tolerated; rapid outpouring of as little as 150 cc. can cause tamponade.† Following pericardicentesis, rapid reaccumulation (Case 1) is typical of pericardial tuberculosis.‡ Effusion is clinically recognized by bilateral increase in cardiac dullness, and, with larger quantities of fluid, even precordial bulging.§ Rubs generally disappear but often persist despite large tuberculous effusions, a phenomenon explained by the persistence of intrapericardial adhesions.‖ Dullness and bronchial breathing below the angle of the left scapula (Ewart's sign) is sometimes present.¶ This is a result of compression of the left lung base by the distended pericardium. On the other hand, Rotch's sign (obtuse cardiohepatic angle) is of doubtful validity, even in the

‖ References 4, 11, and 13.
¶ References 4, 8, 13, and 26.
# References 4, 8, 13, and 26.
* References 4, 8, 9, 13, and 28.
† References 3 and 8.
‡ References 8 and 13.
§ References 8, 13, and 23.

‖ References 3, 4, 8, 13, 30, and 31.
¶ References 3, 6, 8, and 13.
# References 6, 8, 22, and 32.
* References 2, 3, 6, 33, and 34.
† References 12, 13, 34, and 36.
‡ References 13, 16, 22, and 37.
§ References 3, 4, 6, and 13.
‖ References 10 and 13.
¶ References 4 and 13.

enormous effusions seen with this lesion.[3] The potentials of the ECG complexes have no relation to the presence, size, or duration of the effusion, and the effect on them of removal of fluid is variable.[13] One uncommon cardiographic sign, considered pathognomonic of large effusions when present, is simultaneous electrical alternans of the atria and ventricles.# X-ray, fluoroscopy, and kymography, of course, are most conclusive. Straightening of the left cardiac border occurs early, with more definite changes following the outpouring of 300 cc. or more. With large effusions, pulsations appear to decrease or disappear, and the typical pear or flask-shape ensues, often changing with the positioning of the patient. In the absence of pulmonary tuberculosis the pulmonary vascular markings are not increased.*

With the accumulation of a significant amount of pericardial fluid, "pulsus paradoxus" appears (Case 1). This phenomenon is in no way paradoxical. It represents an exaggeration of the normal decrease (5 mm. of Hg) in inspiratory pulse volume † and may be abolished after pericardicentesis [20] (unlike Case 1). This sign should be elicited with the sphygmomanometer, as the smaller ranges may not be palpable.[7] The "paradoxical" beat should have a systolic peak at least 8 mm. below that preceding it.‡

Massive effusion results in cardiac compression. If unchecked, either spontaneously or by treatment, the inevitable result is tamponade, the presence of which may go totally unappreciated.[37] With increasing fluid, all the signs noted increase and are accompanied by visible engorgement of the veins of the upper extremities and head, pulsating distended neck veins, and epigastric tenderness and distention (from physical depression and passive congestion of the liver). Ascites, peripheral edema, and increasing dyspnea may herald the terminal phase in the absence of relief. During the dynamic changes of large effusions, the systolic blood pressure (and with it the pulse pressure) decreases as the venous pressure rises and the precordium becomes "as quiet as a church." With full-blown tamponade, cardiac output reaches insignificant levels.§

Fluid removed in pericardial tuberculosis is almost invariably hemorrhagic—at least during the initial tap (Case 2)—with a lymphocytic differential.‖ As with other serous fluids and exudates, acid-fast bacilli are notoriously difficult to demonstrate, whether by smear, culture, or guinea pig inoculation.¶ Thus, bacteriologic success is reported in from 44% to 71% of cases # and may be quite difficult, even post mortem despite histologic proof.[21] Pneumopericardium, by introduction of air (50% of the volume of fluid withdrawn), illustrates the thickened, shaggy, tuberculous sac wall and the absence of cardiomegaly typical of this lesion (Cases 1 and 2).*

Pathophysiologic Considerations.–Capps[28] investigated the production of pericardial pain by direct stimulation via a cannula, demonstrating that (1) no pain could be produced in the visceral, inner parietal, and upper outer parietal portions of the pericardium; (2) pain could only be produced by stimulation of the outer parietal pericardium at and below the fifth and sixth intercostal spaces. This pain was sharp and referred to the nucha and trapezius ridge. It was thus similar to the pain he obtained from irritation of the central diaphragmatic pleura and was, therefore, of phrenic origin. Since the phrenic nerve enters the cord at the third, fourth, and fifth cervical levels, the area of pain referral is explained. Case 2 is a striking example of this type of pain distribution. Tuberculous pericarditis, as previously

References 3 and 38.
* References 2-4, 8, and 13.
† References 4, 7, 13, and 37.
‡ References 7 and 13.
§ References 4, 13, 27, 37, and 39.
‖ References 8, 12, and 13.
¶ References 4, 10, 12, and 26.
# References 3, 8, 15, and 23.
* References 4 and 12.

noted, may be painless (Case 1) or cause this kind of referred pain. It may also result in chest and/or abdominal pain, both caused by affection of the contiguous pleura.† If the pleuritis involves the peripheral portions of the diaphragm, abdominal pain results; if elsewhere, precordial or even posterior thoracic pain. Simulation of angina results from irritation of efferent nerves in the coronary arteries, causing actual spasm and insufficiency, or, oppositely, of afferent fibers in the periarterial plexuses, resulting in pain interpreted centrally as that of myocardial anoxemia.[29] With compression of the venae cavae, right upper quadrant and epigastric pain results from visceral congestion.[13]

Pulsus paradoxus was first described by Kussmaul.[20] It is in the massive effusion peculiar to tuberculous pericarditis that it is most marked.[37] Katz and Gauchat[20] observed two patients in whom the magnitude of the pressure difference varied directly with the intrapericardial pressure. They further noted that pulsus may occur without changes in ventricular rate, blood pressure, or respiration. In the normal person, inspiratory increase in right ventricular stroke volume results from inspiratory increase in right atrial filling (from negative intrathoracic and positive intra-abdominal pressures). This slightly undercompensates the inspiratory increase in the pulmonary vascular bed; there is thus slightly diminished left heart inflow and therefore slightly decreased left ventricular stroke volume. During expiration the reverse occurs, left heart output becoming slightly more than right.

Two mechanisms have been advanced in explanation of the abnormal pulsus of pericardial effusion‡: (1) Under experimentally increased intrapericardial pressure respiratory changes affect the distended sac proportionally less than they do the thoracic veins. Therefore, inspiratory right ventricular stroke volume is increased less than normally by increased inspiratory venous return. Because of the resultant greater decrease of the left venoatrial gradient, the inspiratory decrease of left ventricular stroke volume is greater than normally. (2) The veins filling the right heart are mostly extrathoracic and therefore mostly not directly influenced by respiratory changes. Right ventricular filling (and stroke volume) increases in inspiration. During effusion, increased inspiratory right ventricular size further increases intrapericardial pressure; this hinders left ventricular filling and therefore left ventricular stroke volume.

The occasional occurrence of electrical alternans in large effusions has been alluded to. This has been ascribed by some to rotatory oscillations of the heart caused by the transmission of the pulse wave in the "spirally arranged" great vessels at its base.[38]

Beck's triad[27] of acute cardiac compression—low arterial pressure, high venous pressure, quiet heart—characterizes cardiac tamponade. This was first studied experimentally in 1889, by Cohnheim,[40] who injected oil intrapericardially, causing increased intrapericardial and venous pressures and decreased peripheral arterial pressure. Maintenance of the same injected volume resulted in stretching of the sac, with slight decrease in its internal pressure and in venous pressure and slight increase in arterial pressure. Barrett and Cole[39] injected water at autopsy into the pericardia of a patient with tuberculous pericarditis and one without pericardial disease and found that it required much larger injected volumes in the tuberculous sac to produce the same pressure changes as in the normal. Evans and co-workers (1950)[34] and Foulger and Foulger (1932)[31] repeated Cohnheim's experiments, using saline. They observed that the same animal could be injected repeatedly seriatim, but progressively more fluid was needed to attain the same pressure. Finally, the normal pericardium is observed to stretch "indefinitely"

† References 28 and 29.

‡ References 13, 31, and 34.

with slowly developing cardiomegaly.[39] The foregoing observations explain the importance of rate of effusion (reflected in pericardial distensibility) in production of tamponade.

Metcalfe[36] and others§ have experimentally confirmed and quantitated Cohnheim's findings with respect to the dynamic effects of steadily increasing intrapericardial pressure. These may be summarized as follows: Increased cardiac compression causes increased mean ventricular diastolic pressure resulting in increased mean atrial and, therefore, venous, pressures. As compression likewise decreases filling, stroke volume drops and with it mean peripheral arterial pressure. (Since peripheral resistance is maintained in tamponade, decreased blood pressure must be due to decrease in *vis a tergo.*) In all of these studies all intravascular pressures eventually approached the same value (about 20 mm. of Hg), at which point circulation ceased. This was a result of progressive decrease in maintenance of normal distribution of blood in the vascular tree. (Pulmonary arterial pressure rose or fell, depending on its initial value, to equal the general level.) All studies demonstrated a critical figure beyond which the drop in mean arterial pressure was rapid. Beyond this point removal of even a few milliliters of intrapericardial fluid resulted in dramatic improvement, correlating well with clinical observations in large tuberculous effusions.[37]

Diagnosis.—Acute tuberculous pericarditis is most often quite difficult to diagnose etiologically.‖ Laboratory proof of Mycobacterium tuberculosis in pericardial fluid is, of course, the only prima-facie evidence. Difficulty of demonstrating this organism in any serous fluid or exudate is well known,¶ and, therefore, its apparent absence should not cast doubt upon the diagnosis in the presence of other clinical evidence.# Stepman and Owyang[12] state that 50% of cases require postmortem confirmation. In numerous series tubercle bacilli were found in widely varying percentages, but never in all cases (often in less than half), despite the authors' diagnostic satisfaction on the basis of other evidence.* No single reported series seems large enough or homogeneous enough, with respect to diagnostic techniques or management, to draw generally applicable conclusions. Apparently the best results were reported by Harvey and Whitehill,[3] whose 37 cases of proved "clinically important" tuberculous pericarditis included 13 in whom fluid was examined during life. Of these, two had tuberculous organisms on smear, one on culture, and five on guinea pig inoculation. Bird† states that organisms would be found in the large majority, were all the fluid subjected to bacteriologic investigation.

Pericardial biopsy has been advised in all cases of pericarditis of obscure cause.‡ Histologic proof would be of undisputed value; however, a negative result could not rule out tuberculosis. Unfortunately, no extensive experience with this method has been reported.

No one hesitates to diagnose tuberculous infection of other serous membranes when other causes can be reasonably excluded.§ When this can be done in a patient with pericarditis, the presence of tuberculosis elsewhere is in favor of the diagnosis (Case 2); nevertheless, it must be remembered that pericarditis as the first clinical sign of active tuberculosis is not rare (Case 1).‖ Any large pericardial effusion is definitely suspect,¶ especially in patients who appear quite well.# The evidence is further enhanced if pericardicentesis, despite

§ References 31, 34, and 37.

‖ References 2, 10, 12, 14, 19, 41, and 42.

¶ References 3, 4, 12, and 19.

References 10, 12, and 21.

* References 3, 8, 10, and 15.

† Bird, K. C.: Personal communication to the author.

‡ References 13 and 14.

§ References 3 and 12.

‖ References 12, 13, and 23.

¶ References 2, 4, and 35.

References 4, 11, 13, and 19.

bacteriologically "sterile" fluid, displays a normal heart size* and a markedly thick, shaggy sac wall after air injection (Case 2).† Three of eleven cases of tamponade assembled by Williams and Soutter[37] were caused by tuberculous pericarditis. These authors also found the pericardial fluid sugar to be decreased over normals during tuberculous effusion.

In the presence of pain, differentiation from myocardial infarction may be necessary on electrocardiographic as well as clinical grounds.‡ RST segment elevations, without "reciprocal" changes, in all or several leads and T-wave negativity only after isolectric return of RST segments are seen in pericarditis. In accord with the views of most other investigators, Keefer[6] gives the following as the main conditions to be excluded: coronary artery disease, congestive heart failure, cirrhosis, and rheumatic pericarditis. He further declares that tuberculous pericarditis should be considered in the presence of irregular fever in patients with heart failure who have signs of pericardial disease. In cases where no other form of pericarditis could be incriminated, specific antituberculous chemotherapy has been employed successfully as a test by Meredith,[2] and also by Goyette,[21] who advocates six weeks of therapeutic trial as a "benign" procedure.

On the basis of the foregoing considerations, in the absence of direct evidence of tuberculosis (positive smear, culture, guinea pig injection, and/or pericardial biopsy), a presumptive diagnosis can be established by reasonable combinations of the following criteria: (1) Exclusion of other causes; (2) Presence elsewhere of tuberculosis; (3) Massive effusion, especially if the patient appears disproportionately "well"; (4) Normal heart size; (5) Post-air-injection roentgenographic demonstration of a thick, shaggy pericardial wall; (6) Response to specific antituberculous agents.

Treatment.—Sixty years ago Sir William Osler[1] defined the objectives in treatment of tuberculous pericarditis as (1) limit the intensity of the inflammation and (2) prevent the evil consequences of large amounts of fluid in the sac. He lamented the absence of "medicinal agents (for) controlling the ordinary inflammations of serous membranes," and stated that an ice bag over the precordium was to be "preferred to the use of blisters or the thermocautery." An early advocate of paracentesis, he recommended free incision and drainage of the pericardium in tamponade, a technique currently advocated by Donaldson.[33]

The advantages of decompression by pericardicentesis have long been obvious.[43] In 1910 this was refined by Wenckebach, who replaced the fluid with air.[4] Others have since stressed the therapeutic value of pneumopericardium, generally claimed on the basis of slowing fluid reaccumulation.§ Thomas[5] held that substitution of an easily compressible gas for a noncompressible fluid was also in its favor. None of these observers has presented more than conjecture in defense of these points; the therapeutic efficacy of air injection remains "at best unproved,"[25] though it is of undisputed diagnostic aid in tuberculous pericarditis.

The formation of a pleuropericardial "window" or extensive pericardiectomy is advocated in cases of failure of other forms of treatment to relieve the acute disease and prevent tamponade or constrictive pericarditis (see below).‖ Herrmann and coworkers[9] favor pericardiectomy even after completion of "successful" medical treatment. It has been repeatedly demonstrated in both humans and animals that this form of surgery carries no undue additional risk even in the face of an acutely diseased membrane.¶ Holman and Willett[32] report healing of all operative wounds by first intention despite active pericardial tuberculosis.

* References 3 and 4.
† References 4, 21, 29, and 42.
‡ References 13 and 29.
§ References 4, 5, and 22.
‖ References 9, 21, 37, 39, and 42.
¶ References 19, 39, 42, and 44.

Since its introduction, streptomycin has been employed in tuberculous pericarditis in a growing number of cases, but most series are, as yet, numerically small.# Striking improvement,* as well as markedly variable results,[42] have been reported. Streptomycin in combination with PAS and/or INH have shown encouraging preliminary results.† Shapiro and Weiss[45] studied 34 clinically comparable cases between 1941 and 1952, of which 20 received antimicrobial therapy and 14 did not. Of the 20, all received streptomycin, 8 were given PAS, and 2, INH. While the authors could draw no long-term inferences, the short-run mortality was cut from 90% to 43% in those receiving specific drugs. They emphasized that, at best, response of this disease to any known form of treatment is slow. The chemotherapy of choice appears to be 2 gm. of streptomycin every third day plus 12 gm. of PAS or 300 mg. of INH daily.‡ In desperate cases all three may be used temporarily (Cases 1 and 2), but the value of an "ace-in-the-hole" in case of bacterial resistance is stressed. Deyke, Fisher, and James[46] have shown that daily exposure to streptomycin results in rapid development of resistant organisms, while intermittent dosage (every third to fifth day) prolongs bacterial sensitivity. It is further advisable to maintain full dosage schedules over a period of 120 days or more and at least 90 days beyond all signs of disease activity.§ Goyette, Overholt, and Rapaport[21] advise bed rest throughout the therapeutic period, followed by progressive ambulation. They offer the following as criteria for inactivity: absence of fever; normal E.S.R.; normal heart shadow and pulsation; stable (not necessarily normal) ECG. These investigators further cite delay in initiating drug treatment and inadequate dosage as reasons for some failures of medical therapy.

References 2, 23, 24, and 42.
* References 25 and 45.
† References 13, 21, and 42.
‡ References 21, 42, and 46.
§ References 21 and 42.

Prognosis.—Ultimate result with regard to life in patients with tuberculous pericarditis is as yet unsettled. The full impact of the specific antiphthisic agents will not be noted before more patients are treated and observed for longer periods. Prior to the current therapeutic era (roughly, before 1950) the outlook was quite poor. Of Harvey and Whitehill's 71 cases,[3] 39 died, as did 18 or 20 reported by Keefer[6] the same year (1937). As late as 1949, up to 85% mortality was recorded.[2] Wood[8] reviewed 41 cases, of which 16 died of pericarditis and 11 eventually from tuberculosis elsewhere. In general, comments on prognosis were typified by "always serious"[6] and "unfavorable . . . most cases fatal within a year."[12]

The major "complication" of tuberculous pericarditis has always been constriction.‖ Indeed, constrictive pericarditis has been termed the "almost inevitable" result.[32] In 61 cases of chronic cardiac compression, Chambliss and associates[27] found tuberculous pericarditis underlying 35% (as against 57.7% due to "unknown causes"). It is not at all rare for the patient to be seen first in the constrictive phase, with no recollection of any acute disease.¶ Other complications are not infrequent and often result in death; these include disseminated tuberculosis,# congestive heart failure (usually secondary to constriction),* and polyserositis (Pick's disease).† Rarely, tuberculous myocardial lesions have resulted.‡

Several factors are fairly reliable prognostic indicators. Striking among these is the actual bacteriological discovery of acid-fast bacilli in the pericardial effusion.[21] In Harvey and Whitehill's series,[3] 81% of cases with this proof of etiology died, as against 5.9% without. Eight of nine patients reported by Myers and Hamburger[23]

‖ References 4, 8, 10, 13, and 27.
¶ References 8, 10, 11, and 13.
# References 3, 6, 13, and 21.
* References 3, 23, and 24.
† References 1 and 6.
‡ References 10 and 29.

died, five of these during the initial hospitalization; in four of the latter, organisms were easily demonstrated. In Wood's review,[8] death claimed 77% of bacteriologically proved, as against 37% otherwise satisfying the diagnostic criteria. Bacteriologically established cases are also more likely to go on to constriction.[27] Even with chemotherapy this remains an adverse factor Case 1).[21]

Age of onset above 50 years carries with it distinctly increased mortality.§ Older patients tend to die either of the lesion or of congestive failure, while younger patients tend more toward disseminated forms of tuberculosis.‖ A gradual, relatively painless onset (Case 1) is distinctly less favorable than sudden, dramatic symptoms (Case 2).¶ Intercurrent cardiac arrhythmias have only been seen in ultimately fatal cases.[8]

The introduction of streptomycin as therapy, and, more recently, PAS and INH, has improved at least the short-run outlook in pericardial tuberculosis. Favorable reports are numerous.# Thus, Myers and Hamburger[23] and McDermott's group[24] report definitely reduced morbidity and prolonged asymptomatic periods. The work of Shapiro and Weiss[45] with streptomycin, PAS, and INH has already been cited. Because of the absence of large series with protracted follow-ups it would be premature to evaluate conclusively the long-term prognosis under "specific" treatment. It is fair, however, to consider current therapy as extremely encouraging.

Summary and Conclusions

A review of the literature is highly suggestive of the not infrequent occurrence of tuberculous pericarditis, first described 104 years ago. This remains a serious lesion, difficult to diagnose and often symptomatically dormant despite the presence of the massive effusions so characteristic of it. Therapeutic success, rare until recently, is not yet assured, despite the hopeful preliminary results with chemotherapeutic agents. Certain factors continue to influence prognosis with or without treatment; these include, notably, mode of onset, age, and ease of bacteriologic proof of etiology. Two cases, fairly typical of the developmental possibilities of the acute lesion, are presented and related to the ensuing discussion. An understanding of the altered dynamics and pathophysiology of pericarditis and cardiac tamponade is emphasized as a key factor in the clinical management of this disease.

§ References 3, 8, and 13.

‖ References 3, 13, and 27.

¶ References 3, 6, and 8.

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Evidence for Increased Venous Tone in Chronic Congestive Heart Failure

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Because venous tone is such an important, unsolved problem concerned with hemodynamic phenomena in congestive heart failure, it was considered desirable to present thoughts and experimental investigations on this subject. The early, important studies of McMichael and Sharpey-Schafer [1] and Starr and Rawson [2] on venous tone in congestive heart failure, as well as the opposing investigations of others,* should be studied by all.

Definitions

1. Congestive heart failure is a clinical syndrome associated with failure of the heart as a pump.

The clinical pattern of ascites, hepatomegaly, generalized systemic venous hypertension, anasarca, bilateral pulmonary basal rales, dyspnea, and other symptoms and signs may have several etiologic associations, but the congestive type of failure of the heart should be considered the cause only when this syndrome is produced by or associated with failure of the heart to pump adequate quantities of blood to the tissues. According to this definition, therefore, congestive heart failure cannot exist without disease or dysfunction of the heart as a mechanical pump.

2. The clinical symptoms and signs of congestive heart failure, although related to failure of the pumping action of the heart, are expressions of many complex physiologic alterations and adjustments.

Failure of the heart as a pump most probably initiates the clinical syndrome of congestive heart failure but cannot in itself produce the entire clinical picture. Subsequent complex alterations in function or physiologic adjustments of the circulatory hemodynamic state, glands of internal secretion, electrolyte and water metabolism, local and general cellular metabolism, kidneys, central and peripheral nervous system, and other organs and tissues ensue, causing retention of electrolytes and water, changes in the distribution of blood volume, and other metabolic alterations.

3. Alterations in function of tissues and organs vary quantitatively.

Alterations in function in congestive heart failure vary to produce quantitative differences in the clinical and physiologic expressions of the disease. Relative differences may not be large, but, qualitatively, congestive heart failure is a single physiologic state.

4. The rate of change and duration of the physiologic alterations vary quantitatively.

Quantitative variations in the clinical manifestations are also attributable to differences in degree, rate of development, and duration of the physiologic alterations consequent to degree, rate, and duration of failure of the heart to pump adequate quantities of blood, at least to certain vital tissues.

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* References 3 and 4.

5. The time courses of phases of the disease and of failure of the heart vary.

The relationship of the physiologic alterations to the clinical manifestations depends upon many factors, including the stage of the disorder, i. e., whether or not it is progressing or regressing and the rate of change of the failure, as well as its duration and severity. Failure to define these variables precisely may result in apparent differences being considered real. For example, anasarca in progressive failure of the pumping action of the heart correlates differently with the physiologic state than does anasarca in regressing failure, the general physiologic states differing greatly even though the anasarca may not differ chemically.

Theoretic Hemodynamic Considerations in Congestive Heart Failure

On the assumption that the physiologic and clinical syndrome of congestive heart is initiated by failure of the heart as a pump, the hemodynamic consequences will be considered, with special emphasis on the venous system.

Proposition I.—Given a distensible, horizontally located, continuous, circular, tubular system containing a liquid, such as water or blood, unidirectionally circulated by a single pump, failure of the pump will not cause the liquid to accumulate unevenly in volume within any part of the circuit.

Suppose pump, *P*, circulates water in a clockwise direction in a circular, horizontal, open moat, *acv*, of uniform depth and width (Fig. 1*A*). Because of frictional factors, as long as the pump provides sufficient energy to the system, the liquid will continue to circulate. Let the pump fail to provide energy, and the liquid will come to rest with equal volume distributed throughout the moat because gravitational and atmospheric forces act uniformly upon the liquid throughout (Fig. 1 *B*).

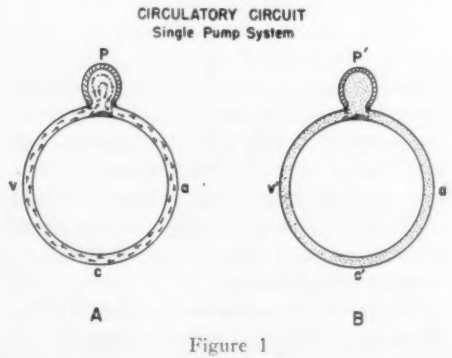

Figure 1

As in the open moat, so in a closed, continuous, horizontally located, distensible tubular system, *acv*, filled with a liquid, as water or blood, circulated by single pump *P*, (Fig. 2), the liquid will come to rest

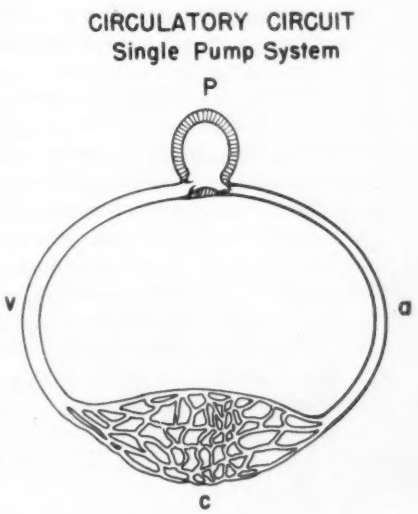

Figure 2

evenly distributed under equal pressure because of frictional factors, should the pump fail to provide energy for circulation. Liquid will not, therefore, accumulate disproportionately at relatively high pressure in portion *v* or any other segment.

Proposition II.—Given a distensible, horizontally located, continuous, circular, tubular system containing a liquid, as water or blood, unidirectionally circulated by two pumps of equal output but separated from each other by a relatively small and a relatively larger segment of the circulatory cir-

cuit, failure of the pump P in expelling liquid from the smaller segment to the larger one will cause pump P' to distend the small segment relatively greatly, whereas failure of pump P' in expelling liquid from the larger segment into the smaller segment, will cause pump P to distend the large segment relatively little.

Suppose a circular, horizontally located open moat of equal width and depth and composed of segments S' and S, the latter nine times the size of the former, contains water circulated by two pumps, P' and P, which simultaneously pump equal volumes of water to produce clockwise flow; then a steady state of flow with equal volumes of water per unit length of moat will be maintained as long as the two pumps function equally. Should P pump a unit volume less liquid per stroke than P', then water will accumulate in smaller segment S', overfilling or flooding (depending upon fluid quantities and capacities of S') this segment with water pumped from larger segment S. On the other hand, should P' pump one unit volume less liquid per stroke than P, then smaller segment S' will eventually be emptied into larger segment S, with relatively less overfilling or flooding of S and, finally, the volume output of pump P will become equal to and be determined by the volume output of pump P', for no more water can be pumped from S' than is present in that segment.

As in the open moat, so it must be for the distensible tubular circulatory circuit of man. Merely substitute the pulmonary circulation, with a blood volume of about 500 cc., for smaller segment S', and the systemic circulation, with a blood volume of 4500 cc., for larger segment S, the left ventricle for pump P, and the right ventricle for pump P' (Fig. 3). Thus, if P pumps less blood than P', overfilling of the distensible pulmonary circulatory system will readily be achieved because of its relatively small capacity and the relatively large volume of blood in the systemic vascular system from which to draw. If, on the other hand, P'

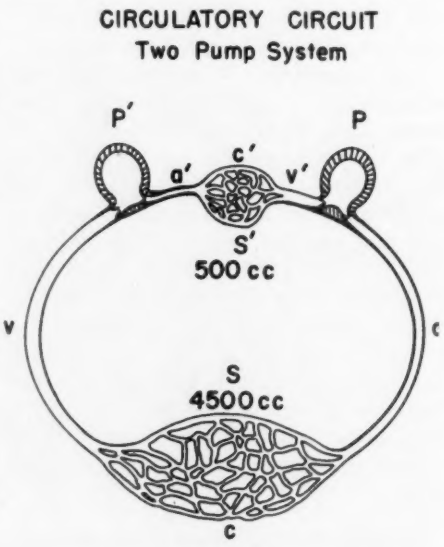

Figure 3

pumps less than P, then, by similar reasoning, the larger distensible systemic circulatory system will not be greatly overfilled with blood and the volume pumped by P' will determine that pumped by P.

Proposition III.—Given a distensible, horizontally located, continuous, circular, tubular system containing a liquid, as water or blood, unidirectionally circulated by two pumps of equal output but separated from each other by a relatively small and a relatively larger segment of the circulatory circuit, failure of the two pumps equally and simultaneously will cause the liquid to come to rest with the same distribution as found during the circulating state.

Suppose the liquid were flowing in a moat with pumps P and P' arranged as shown in Figure 3 and as indicated in Proposition II, then equal and simultaneous failure of the two pumps will not cause unequal distribution of the liquid but will result in the same volume distribution at rest as existed when the liquid was flowing. The net result is as found for a single pump system, indicated in Proposition I.

Corollary I: Because of the nature of the function of the valves in the continuous cir-

culatory systems discussed (including the heart of man), stoppage of the pumps will result in pressure equalization throughout the circulatory circuit, including the small segment, with necessary volume distributions of the contained fluid to compensate for unequal distensibilities and volume capacities to achieve equality of pressure throughout the circulatory circuit.

Proposition IV.—Given a distensible, horizontally located, continuous, circular, tubular system containing a liquid, as water or blood, unidirectionally circulated by a single pump, if the tubular system or circuit is suddenly and completely obstructed as the intake side of the pump, the liquid will come to rest with equal and uniform distribution in the circuit as existed during circulation.

Suppose pump, *P*, is circulating water in a clockwise direction in a horizontally located moat, *acv*, of uniform width and depth and suddenly the circuit is completely obstructed at the intake opening of the pump indicated by arrow, *O* (Fig. 4*A*); then the pump will

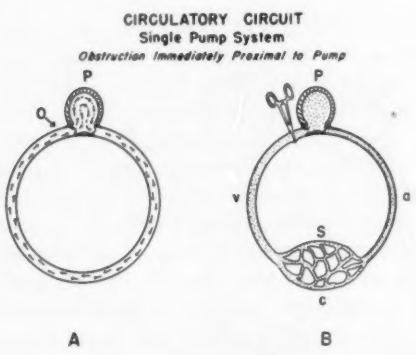

Figure 4

cease to aspirate water and impart energy to flowing water. Because of frictional resistance, the water will come to rest with the same volume distribution throughout the moat as existed prior to obstruction to flow into the pump.

The same equal distribution of the liquid would ensue if the circulatory system were constructed of continuous, distensible, horizontally located tubes, such as blood vessels, and if obstruction occurred at the intake opening of the pump. Liquid would not accumulate in unequal amount at the point of obstruction (Fig. 4*B*). Unequal distribution of liquid, regardless of its nature, would be due to forces emanating from within the walls of the distensible tubular system.

Proposition V.—Given a distensible, horizontally located, continuous, circular, tubular system containing a liquid, as water or blood, unidirectionally circulated by two pumps of equal output but separated from each other by a relatively small and a relatively larger segment of the circulatory circuit, sudden and complete obstruction of the circuit at the intake side of the pump, expelling liquid from the small segment, will cause overfilling or flooding of the small segment and will tend to empty the large segment.

Suppose a forceps suddenly interrupts the flow of a liquid from a 500 cc. segment, *S'*, then the output from pump *P* will suddenly stop because of lack of inflow, but pump *P'* will continue to discharge liquid from the 4500 cc. segment, *S*, into segment *S'*, with resultant overfilling of small segment *S'*, which is unable to accommodate the entire volume of liquid from *S* (Fig. 5).

Corollary I: The less distensible the walls

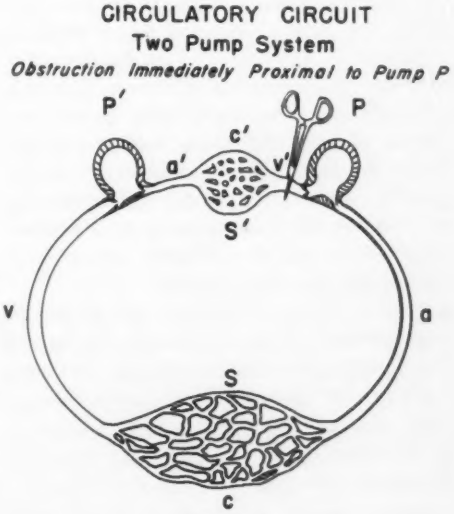

Figure 5

of segment S', the less volume it will accommodate per unit rise in pressure and the greater will be the rise in pressure per unit volume of fluid injected into it.

Corollary II: The volume distribution of liquid accommodated by various portions of segment S will tend to vary directly with the distensibility of respective portions. For example, if portion v is more distensible than portion a, then more of the liquid ejected by P into segment S will find its way into v than into a.

Proposition VI.—Given a distensible, horizontally located, continuous, circular, tubular system containing a liquid such as water or blood, unidirectionally circulated by two pumps of equal output but separated from each other by a relatively small and a relatively larger segment of the circulatory circuit, sudden and complete obstruction of the circuit at the intake sides of the pump, expelling liquid from the larger segment into the smaller segment, will cause emptying of the small segment without necessarily overfilling the large segment.

Suppose a forceps suddenly interrupts the flow of the liquid from segment S into pump P'; then the output of liquid by P' into the small 500 cc. segment, S', will cease, whereas pump P' will continue to remove liquid from segment S' until its contents are emptied into the larger 4500 cc. segment, S, provided S is sufficiently distensible to accommodate, without difficulty, the extra liquid displaced from smaller segment, S' (Fig. 6). It is evident that the size and degree of distensibility of the respective segments S' and S will determine the volume of liquid these systems will accommodate and the resultant pressures of the liquid contained therein.

Corollary I: The less distensible the tubular walls of segment S, the less volume of liquid it will accommodate and the higher will be the rise in pressure within the system per unit volume of liquid forced into it.

Corollary II: The volume distribution of liquid in the various segments of the circulatory circuit will tend to vary directly

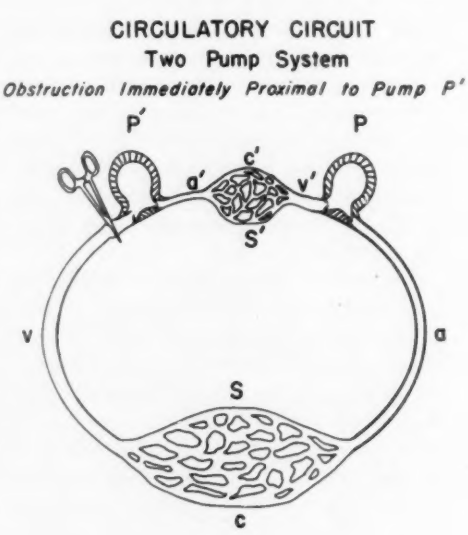

Figure 6

with distensibility of the respective portions of segment S. For example, if the v portion is more distensible than the a portion, then more liquid will be distributed in v than in a.

Corollary III: The quantity or volume output of a pump is limited by the quantity or volume intake. Thus, limitation of intake will cause limitation of output.

Comment.—For living man it becomes evident that, hemodynamically, a "dam in the stream" located behind the left ventricle (pump P) will produce congestion of the pulmonary vascular system, S', with blood. The amount of blood that can be "dammed" behind the right ventricle, on the other hand, is relatively small and limited. It would not likely exceed 500 cc. and would reach this extent only if all the blood in the pulmonary vessels could be removed by the left ventricle and ejected into the systemic vessels, S. All the blood cannot be so removed, however, for this would be incompatible with life itself.

In these discussions related to the distensible and complex tubular circulation of man, it is assumed that the lumens of the entire vascular system are open and continuous at all times. Closure of any segment causing

discontinuity in the lumen of the circulatory circuit will modify the conditions and interpretations. Vasomotor and passive recoil or "elastic" characteristics of the components of the wall of the vascular system, gravitational forces, and other extravascular forces likewise can independently modify the conditions discussed in the foregoing propositions and corrollaries.

Proposition VII.—Given a closed, distensible, horizontally located, continuous, circular tubular system containing only a liquid, as water or blood, with a wall capable of tightening or loosening, the pressure within will rise or fall, depending upon variations in tightness of the wall, with little associated volume change because the liquid is relatively incompressible for the pressure considered.

Suppose distensible tubular system *SS'S"* contains only an incompressible liquid; then the volume of the lumina of the tubular system will be equal to the volume of the liquid within (Fig. 7).

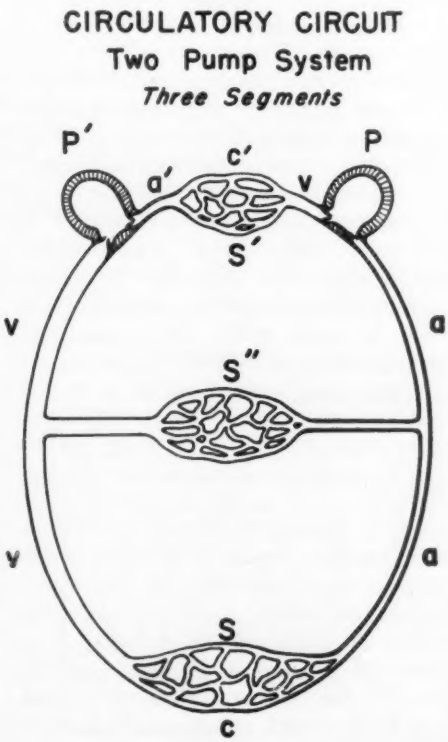

Figure 7

1. If the molecular components of the wall tend to shorten equally, uniformly, and with equal effective tension throughout, the volume of the system will not change, but the pressure of the liquid within will rise, and the tubular wall will fit more tightly around the liquid within.

2. If the molecular components of the wall tend to lengthen equally and uniformly throughout, the volume of the tubular system will not increase nor will the liquid within expand, but the pressure of the liquid within will decline, and the tubular wall will fit less tightly around the enclosed liquid.

Corollary I: If the molecular components of the wall in any one portion of the distensible tubular system shorten and there is a local decrease in tubular luminal volume with displacement of liquid to another site in the tubular system, then there will be an increase in volume with lengthening of the molecular components of that portion of the wall to which the liquid was displaced. Thus, if the volume of *S'* decreases by 10 cc., then the volume of *S'* or *S"* must increase by 10 cc. or both must increase by a total of 10 cc. to accommodate the displaced liquid (Fig. 7). The pressures throughout may or may not change, depending upon the state of tension of the tubular walls.

Corollary II: If the molecular components of any one portion of the wall of the distensible tubular systems lengthen, the volume will increase locally and the liquid will be displaced into that portion. An equal volume will be removed from another area of the system, where there will be an equal decrease in volume and corresponding shortening of the molecular components of the wall of this portion. Thus, if there is dilatation of segment *S'* of the tubular system with an increase in volume of 10 cc., 10 cc. of liquid will move into this segment with a decrease in volume of segment *S* or *S"* by 10 cc. or a decrease in both by a total of 10 cc. (Fig. 7). The pressure may or may not

change, depending upon the state of tension of the tubular walls.

It is evident from these arguments that in an enclosed, distensible, tubular system, such as the cardiovascular system, filled with a relatively incompressible liquid, such as blood, the pressure within can change over wide ranges as a result of variations in the "tightness" with which the wall squeezes upon the enclosed liquid, while the volume of the liquid and lumen of the system can change relatively little.

The volume of the lumen of such a system filled with a liquid will at all times equal the volume of the liquid within. There can be no absolute disproportion in volume of liquid and volume of the system under such conditions.

Proposition VIII.—Given a closed, distensible, horizontally located, tubular system with the lumina continuous throughout and containing only a liquid, as water or blood, the volume of which is capable of being varied, the pressure within will tend to rise with an increase in volume of the liquid and will tend to decline with a decrease in volume.

Suppose distensible system *SS'* contains a given volume of incompressible liquid so that its luminal volume is equal to the volume of the liquid; then an increase in volume of the liquid produced by injection of more liquid into the system will distend the walls of the system and increase the pressure of the system within, whereas removal of some of the liquid will reduce the pressure (Fig. 8). These pressure changes will occur because, with stretching of the distensible wall, the structures of the wall will offer counterresistance to distension and thereby squeeze upon the liquid within, increasing its pressure. The reverse would be true with removal of liquid. The degree of pressure change per unit volume change will depend upon the physical characteristics of the components of the walls of the cardiovascular system.

Corollary I: The degree of rise in pressure associated with an increase in volume of intraluminal liquid will be directly related to the degree of resistance to distension offered by the distensible wall. The greater this resistance, the greater will be the rise in pressure per unit change in liquid volume.

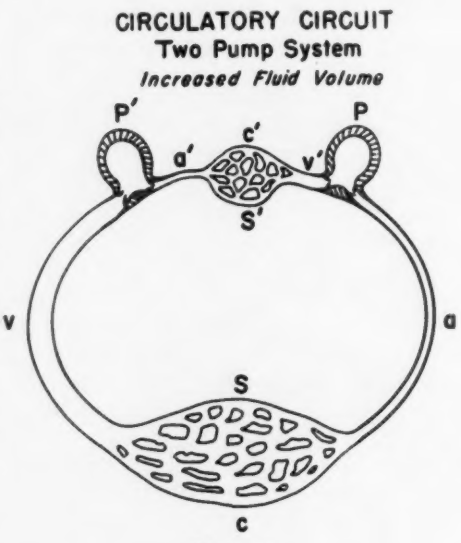

Figure 8

Corollary II: Any alterations in or resistance to distensibility as liquid volume is changing will be associated with modification of the pressure changes. This may be exemplified differently, i. e., if the wall of the distensible tubular system has a given capacity to distend and at the same time offers an equal counterforce per unit area of wall upon the liquid within, the pressure will remain unchanged as liquid volume changes.

Living systems, such as blood vessels, the walls of which contain smooth muscle, are particularly designed to vary the physical state of the muscle so that the walls fit more tightly or more loosely around the blood within or are capable of changing or maintaining a given degree of tightness in spite of variations in the volume of blood within the vascular system. Such variations in tension of the smooth-muscle elements will influence the pressure of the liquid contained therein; thus, factors that modify the tension of the smooth muscle will, in turn, influence intraluminal pressure.

The heart is a segment of the distensible, closed, circulatory circuit and, therefore, participates in the interrelation of intraluminal pressure and volume already discussed. Cardiac muscle mass functions as the source of mechanical energy with contraction and relaxation of its fibers. The time course of and the degree of tension determine the time course of intraluminal cardiac pressure. Normal and abnormal valvular function will likewise vary the temporal relationships of intraventricular volume and pressure, as well as tension of the ventricular wall.

Observations Related To Venous Tone In Chronic Congestive Heart Failure

Selected observations in this laboratory that reflect the state of venous tone in subjects with chronic congestive heart failure will be discussed.

Systemic Venous Pressure

Systemic venous pressure has been measured directly the world over [5] on many occasions in several veins of the extremities and body surface of subjects with chronic congestive heart failure. The venous pressure is increased and, in general, tends to vary as indicated in Figure 9. The state of distension of the cervical veins of subjects with congestive failure reflects the variations in venous pressure. The presence of the venous hypertension deserves consideration as evidence of the state of venous tone. From the propositions made earlier in this report, it is evident that with higher pressure of the blood within the veins, the counterforce offered by the venous wall to support this pressure is increased, for

$$F=P\times A, \qquad (1)$$

where F is force, P, pressure, and A, area. Thus, with an increase in pressure within the venous lumina, the total force against the venous wall is increased, that is, if the area of the venous wall has not decreased significantly. If there is a change in diameter of the veins, the force per unit length of vein will vary accordingly (Equation 1).

The force offered by the venous wall in support of the pressure within is expressed by the equation

$$F=2rP \qquad (2)$$

$$T=rP, \qquad (3)$$

where T is the tension on the molecules of the venous wall in dynes per unit length (centimeters), P the intravenous pressure in dynes per cubic centimeter, and r the radius of the vein in centimeters. The origin of the equation (3) is evident from Figure 10, showing half of a cross section through a venous segment. A unit length (1 cm.) of venous wall is supporting a force that can be visualized as acting upon the imaginary plane shown with an area of $2r1$ or $2r$, since 1 is unity. The force offered by the wall is supplied by the smooth

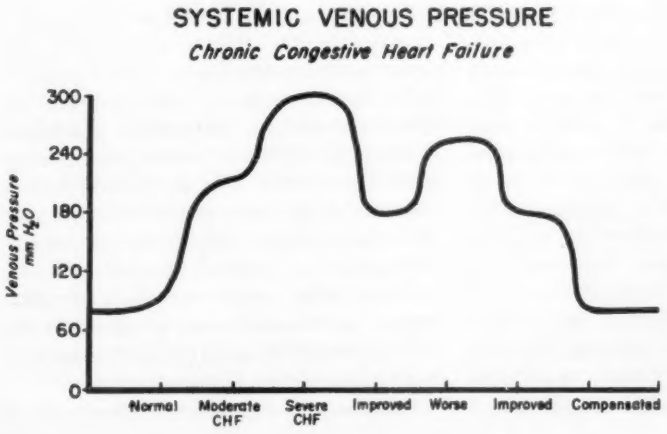

Fig. 9.—Changes in venous pressure associated with variations in severity of congestive heart failure. The level of the venous pressure tends to vary directly with the degree of congestive failure. (Reproduced with permission from Burch, G. E.: A Primer of Venous Pressure, Philadelphia, Lea & Fegiber, 1950.)

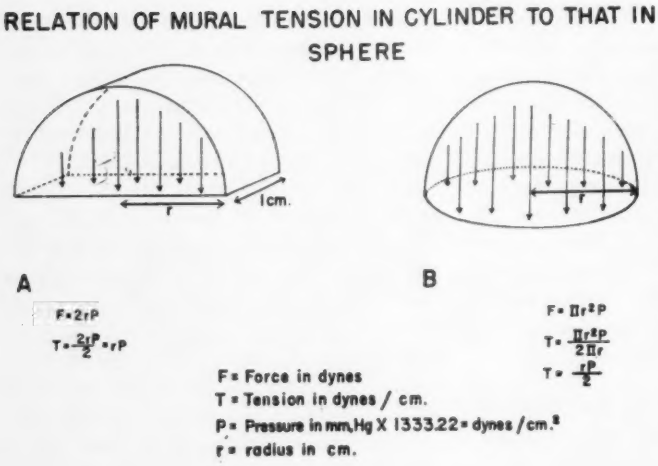
RELATION OF MURAL TENSION IN CYLINDER TO THAT IN SPHERE
r
1cm.
A
B
F = 2rP
T = 2rP / 2 = rP
F = πr²P
T = πr²P / 2πr
T = rP / 2
F = Force in dynes
T = Tension in dynes / cm.
P = Pressure in mm.Hg X 1333.22 = dynes / cm.²
r = radius in cm.

Fig. 10.—Illustration showing that tension in the wall of a cylindrical structure, such as a blood vessel or vein, varies directly with the product of the radius and intraluminal fluid pressure, whereas the tension in the wall of a sphere varies directly with half the product of the radius and intraluminal pressure. Thus, the tendency for the heart to be spherical in shape is an advantage from the point of view of mural tension that must be developed during myocardial contraction.

muscle fibers and other structures that constitute the venous wall. This tension or force offered by the wall increases or decreases with (1) increase or decrease, respectively, in intraluminal pressure and (2) increase or decrease, respectively, in diameter of the vessel unless the wall ruptures or disintegrates. As long as the vessel is filled with blood, the force offered by blood against the venous wall is counterbalanced by an equal force derived from the molecules that form the venous wall.

When the venous pressure increases, the tension in the wall of the vein also increases. The question is whether or not this increase in tension is borne passively only by such structures as elastic and fibrous connective tissue and smooth muscle, which form the greatest mass of tissue in the venous wall, or whether the smooth muscle fibers actively support some of the force, in part, by a state of active contraction. It would be most unusual to expect the smooth muscle to participate only passively, especially when its function in supporting the pressure within all intact vessels is considered to be active under other circumstances. However, once the molecular state and configuration of the smooth muscle have been set, the quantity of energy required to maintain the new state may be extremely small, vasodilating or vasoconstricting stimulation being needed to change the state to another one and energy of metabolism being essential for the production of the other state, especially if it is concerned with a tendency for the smooth muscle to shorten. Smooth muscle has the capacity to maintain relatively high tension at different fiber lengths. A vein could be distended, with high pressure within, or narrowed, with the same pressure within, and the smooth muscle might be actively "contracted" or tense with equal tone or tension, an expression of active metabolic phenomena. It may be noted that a time factor enters in such a definition of active metabolic tone, that is, the state must be maintained for a relatively prolonged period of time.

That the systemic venous system is under increased tone is strongly supported by the rapid and sharp decrease in venous pressure following intravenous administration of hexamethonium, a sympathetic ganglionic blocking agent. Were venous pressure only passively elevated with the tension in the venous walls passively increased but without the smooth muscle tone, a tension actively increased as a result of metabolic activity, hexamethonium would not likely decrease venous pressure and cause a collapse in the neck veins of the subjects with congestive heart failure in the sitting position.

That the more centrally located veins, such

as the cervical veins, are dilated is not necessarily indicative of less venous tone in these veins. The tone or tension offered actively by the smooth muscle of the veins of the neck could be increased over the normal state. With generalized systemic venous hypertension, blood would be expected to be displaced to the large, centrally located veins because of simple hemodynamic principles based upon Laplace's law.

Since $F=PA$, (1)

then if pressure is essentially equal throughout the systemic venous system, the smaller peripheral veins will support a smaller force per unit length of vein than will the larger, centrally located veins, everything else being equal. For example,

(1) The walls of central vein of 10 cm. length and 10 mm. diameter with intravenous pressure of 200 mm. H_2O will support a total force of

$F=20\times2\times3.1416\times0.5\times10\times980.6=616{,}130$ dynes

(2) The walls of peripheral vein of 10 cm. length and 0.1 mm. diameter at 200 mm. H_2O intravenous pressure supports a total force of only 6161 dynes.

Thus, smooth muscle in a small peripheral vein may need to develop relatively little force to constrict and readily displace blood into the larger, centrally located veins, even though they may be under an increased state of tension and contracting against the same pressure. The relationship of tension or force per unit fiber for vessels of various diameters and with different intravascular pressures needs careful study.

The state of the sympathetic nervous system and the role of chemoadrenergic factors in maintaining and varying smooth muscle tone also need study, not only in congestive heart failure but in other states as well. During periods of congestive heart failure, the tachycardia, profuse sweating, pallor of the skin, increase in arterial blood pressure, and increase in systemic venous pressure may all be expressions of increase in sympathetic nervous systemic activity.

Although the increase in venous pressure in congestive heart failure does not necessarily indicate greater tension of the smooth muscle in the venous wall, it is more likely that the smooth muscle tension or tone is high and that the smooth muscle fibers are actively contributing to the support of the high pressure rather than being in a state of passive distention like the other structures of the wall. This is particularly true in view of the action of intravenously administered hexamethonium.

Hepatojugular Reflux

When pressure is applied to the hepatic area of normal man, the pressure in the median basilic vein in the antecubital area rises slightly (less than 20 mm. H_2O), not at all, or even declines from the level prior to application of pressure (Fig. 11). On the other hand, when pressure is applied to the hepatic area of a subject in congestive heart failure with systemic venous hypertension, the pressure in the median basilic vein invariably rises more than 20 mm. of H_2O pressure (Fig. 12). The difference in response of the normal subject and the one

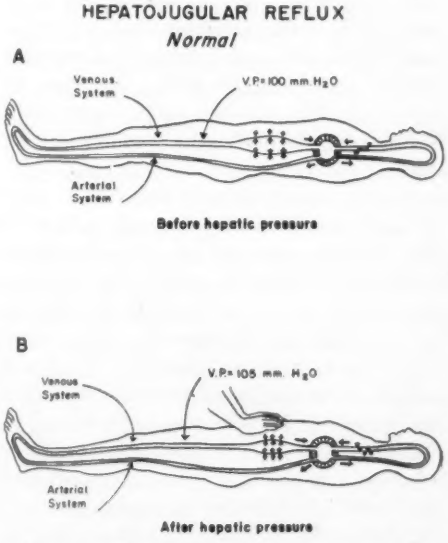

Fig. 11.—Diagrammatic representation of the failure of manual pressure over the hepatic area to increase the pressure within the systemic veins in a normal subject with a less "tight" venous system and of a more resilient venomotor and sympathetic venomotor state.

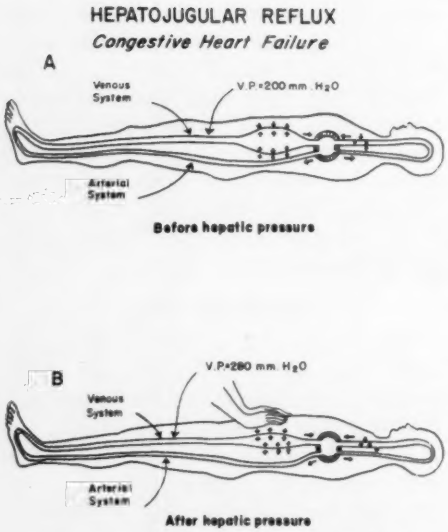

Fig. 12.—Diagrammatic representation of the increase in systemic venous pressure produced by the application of manual pressure over the hepatic area in a subject with active chronic congestive heart failure. Apparently this is due in part to a "tight" venous system with an increase in venomotor tone and less resilient sympathetic venomotor state.

with congestive heart failure is related in large part to the difference in the state of tone of the smooth and sympathetic nervous system activity muscle in the two types of subjects.[7] This response may be interpreted to support the following venophysiologic state.

In the normal subject the venous tone or state of tension of the smooth muscle in the systemic vein and the venophysiologic state, which include sympathetic nervous system activity, are so aranged to insure an an essentially uniform systemic venous pressure despite wide variations in total blood volume or venous blood volume and despite the tendency for the venous pressure to fluctuate. One-half to more than one liter of blood may be transfused into normal man with relatively little rise in venous pressure. Similarly, 500 to 1000 cc. of blood may be removed from the vascular system of normal man with relatively little change in systemic venous pressure. Thus, the volume of the venous system can vary within wide range with little change in venous pressure. Therefore, venous tone or the active tension of the smooth muscle of the venous system, or the tightness with which the walls of the veins squeeze upon the blood within, is normally arranged to remain fairly constant in spite of wide variations in the volume of blood contained therein.

This unique adjustment of tension of smooth muscle in the veins of normal man must be mediated in part through the sympathetic nervous system, the chemoadrenergic system, and possibly local venobaric mechanisms, all little studied and poorly understood. In the subject with congestive heart failure, the dynamic state of the veins appears to be functionally altered.

Firstly, the venous pressure is high and the tone of the smooth muscle within the walls of the veins is most probably high, as already indicated.

Secondly, the volume of the veins can vary relatively little without extreme change in venous pressure. For example, transfusion of less than 500 cc. of blood into a subject with congestive heart failure increases venous pressure considerably and produces an acute exacerbation in the state of failure. Removal of 500 cc. of blood, a common therapeutic procedure, not only produces improvement in the clinical state but reduces venous pressure greatly.

Thirdly, an increase in venomotor tone increases venous pressure in a local organ or structure to an extent greater than occurs in normal man. For example, clenching of the fist or contraction of the muscles of the legs or thighs increases the pressure in the veins of the arm or leg, respectively, to a degree greater than occurs in the normal subject. This is a phenomenon analogous to pressure applied over the hepatic area.

Fourthly, it has been found that intravenous administration of hexamethonium, a sympathetic ganglionic blocking agent, reduces systemic venous pressure greatly in subjects with congestive heart failure in association with dramatic improvement in the clinical state (Fig. 13). After admin-

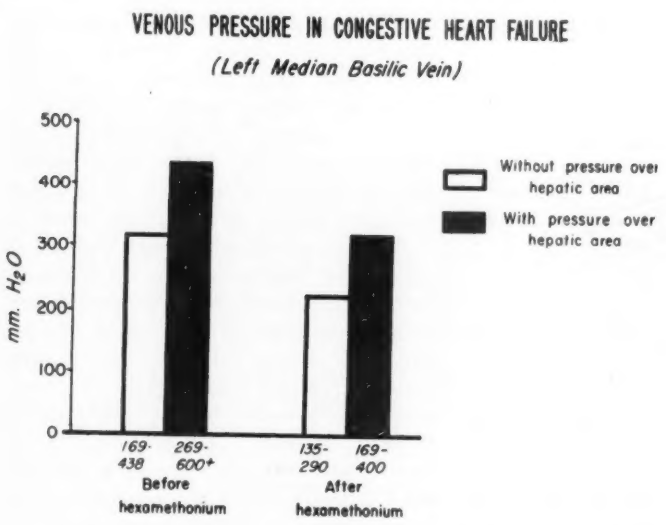

Fig. 13.—Influence of hexamethonium upon the systemic venous pressure with and without pressure over the hepatic area in subjects with chronic congestive heart failure. (Reproduced with permission from Burch, G. E.: A. M. A. Arch. Int. Med. 94:724 [Nov.] 1954.)

istration of hexamethonium, pressure over the hepatic area still causes venous pressure to rise but to a lesser degree than prior to its administration. This response is compatible with a loosened venous system and reduction in activity of the sympathetic nervous system, which is probably responsible in large part for the increase in tone of the smooth muscle of the vein in congestive heart failure. For the smooth muscle to become less tense after administration of hexamethonium, the muscle must have been in a state of increased active tension or tone in the first place.

These venous phenomena are compatible with alterations in venous function in association with increased tone or tension of the smooth muscle in congestive heart failure. Although such reactions might conceivably exist in a passively distended, nonrigid vascular system, the nature of the functional state is certainly compatible with alterations in venous function to insure high smooth muscle tone produced by one, or a combination of, the following factors: Increased activity of the sympathetic nervous system, increased adrenergic and other chemical activity, or local and general venobaric activity. The mechanism for the increase in activity of the sympathetic nervous system may be due to inadequate cerebral blood flow, as suggested over 50 years ago by Starling.[6]

Digital Venous Tone

Digital venous tone has been studied rheoplethysmographically [8] in chronic congestive heart failure [9] with the use of a sensitive pneumoplethysmograph and the venous occlusive method for recording digital flow. The time courses of volume, rate, and acceleration in rate of digital inflow, outflow, and difference between inflow and outflow were recorded simultaneously and continuously during a single pulse cycle. This was achieved by enclosing the fingertip in a plastic plethysmographic cup and recording plethysmographically the time course of the change in finger volume following controlled occlusion to venous outflow (Fig. 14). A typical rheoplethysmogram for a normal subject is shown in Figure 15. Invariably, the rheoplethysmogram of the subject with congestive heart failure revealed low rates of digital inflow and outflow (Fig. 16). Despite a decidedly lower rate of digital inflow (I_R), the venous reservoirs were unable to accommodate as much blood as in the normal subject, as evidenced by the more rapid build-up of pressure in the digital

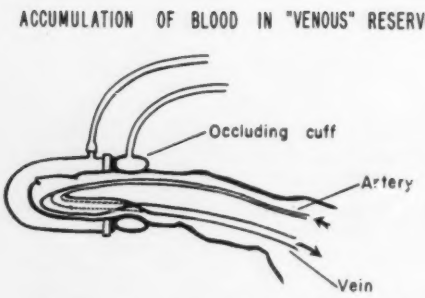

Fig. 14.—Diagrammatic representation of the plethysmographic cup and cuff in place for a rheoplethysmographic recording, showing how inflation of the occluding cuff results in trapping of inflowing blood in the digital veins where it is measured. (Reproduced with permission from Burch, G. E.: A. M. A. ARCH. INT. MED. 94:724 [Nov.] 1954.)

veins in excess of the pressure within the occluding cuff, with resultant accumulation of less blood in the digital venous reservoirs and leakage past the occluding cuff (Fig. 16). This leakage is demonstrated by the erroneous rheoplethysmographic (Fig. 16) recordings of absence of digital flow, for occlusion to venous outflow at that same moment in other similar pulse cycles revealed digital flow to exist.

These observations merely indicate a tight digital vascular system. The low rate of inflow must reflect arteriolar constriction, but the tight venous reservoir may be interpreted as evidence merely of a passively distended and a tight digital venous system and not necessarily an increase in active digital venous tone or greater active tension of the smooth muscle. For the purpose of determining whether or not smooth muscle tone was increased, hexamethonium, a sympathetic ganglionic blocking agent, was injected intravenously in the subjects with congestive heart failure while the rheoplethysmograms were being recorded. A decrease in systemic venous pressure was observed, with less rise in venous pressure when manual pressure was applied over the hepatic area, as described previously. In addition, total digital blood volume increased and, despite an increased rate of digital inflow (Fig. 17), there was less rapid overfilling of the venous reservoir or leakage past the occluding cuff. There was also an increase in volume of the digital vascular bed, which included the digital veins.

These findings indicate a reduction in

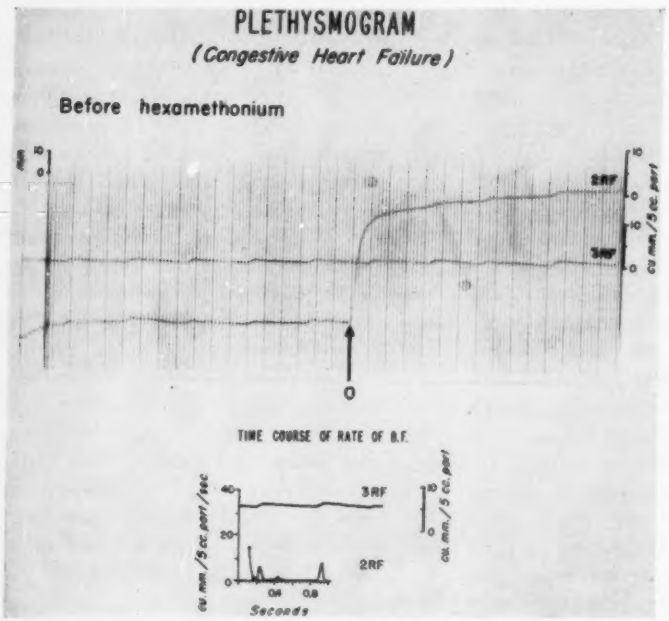

Fig. 15.—Rheoplethysmogram, showing low rate of digital blood flow and rapid overfilling of "tight" digital veins with early leakage past the occluding cuff prior to the intravenous administration of hexamethonium to a subject with chronic congestive heart failure. (Reproduced with permission from Burch, G. E.: A. M. A. ARCH. INT. MED. 94:724 [Nov.] 1954.)

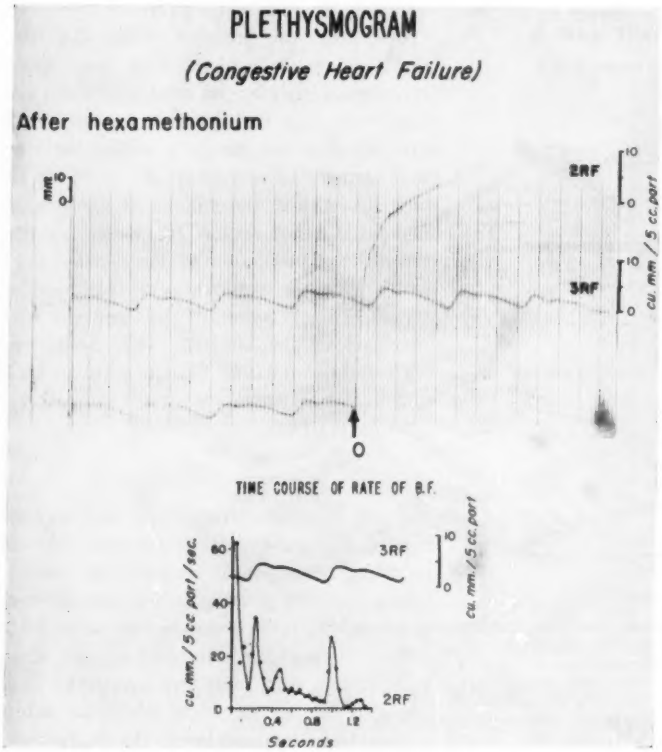

Fig. 16.—Rheoplethysmogram showing a great increase in the rate of digital blood flow and more readily distensible or less tight digital veins in the same subject shown in Figure 15 shortly after the intravenous administration of hexamethonium. (Reproduced with permission from Burch, G. E.: A. M. A. Arch. Int. Med. 94:724 [Nov.] 1954).

smooth muscle tone by the drug in all digital vessels, not only of the arterioles but of the veins as well. For active tone to exist in the presence of high venous pressure, there must be a state of high smooth-muscle tension in the digital veins in the subjects with chronic congestive heart failure.

Venous Tone in Superficial Venous Segments of the Forearm

Small venous segments of selected superficial veins on the forearm of subjects were isolated from the remainder of the venous system for study by means of small brass wedges, as shown in Figure 19.[19] An effort was made to demonstrate the absence of tributaries to the isolated venous segment by pressing gently on the segment and showing failure to squeeze blood out of the segment through connecting tributaries. Furthermore, during the experiments the pressure within the segment varied independently above the level of the systemic venous pressure. Small tributaries in the form of venae vasorum may have existed, but the nature of the changes in pressure within the isolated segment and the veins outside the segment suggested either that they were absent or, if present, that they were so slight as to have no significant influence on the results.

The time course of the pressure in a typical venous segment in a subject with congestive heart failure is shown in Figure 20. The segment was so prepared that the pressure within, with the subject at rest, exceeded that in the nonisolated systemic venous system. Pressure upon the hepatic area caused the venous pressure to increase. This response must have been mediated in large part, at least, through the sympathetic nervous system, since the segment was isolated from the remainder of the systemic

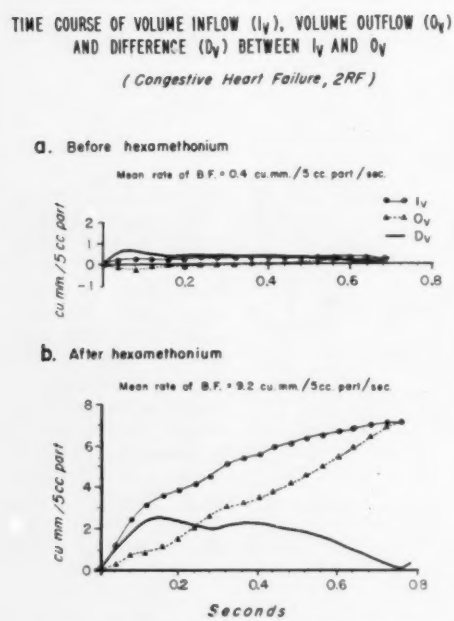
TIME COURSE OF VOLUME INFLOW (I_V), VOLUME OUTFLOW (O_V) AND DIFFERENCE (D_V) BETWEEN I_V AND O_V
(Congestive Heart Failure, 2RF)
a. Before hexamethonium
Mean rate of B.F. = 0.4 cu.mm./5 cc. part/sec.
I_V
O_V
D_V
cu mm./5 cc. part
b. After hexamethonium
Mean rate of B.F. = 9.2 cu.mm./5cc. part/sec.
cu mm./5cc part
Seconds

Fig. 17.—Time-course curves of the volumes of inflow (I_V), outflow (O_V), and the difference (D_V) between I_V and O_V during a single-pulse cycle for the same subject and pulse cycle shown in Figures 15 and 16 before and after the intravenous administration of hexamethonium. (Reproduced with permission from Burch, G. E.: A. M. A. Arch. Int. Med. 94: 724 [Nov.] 1954.)

veins. With release of pressure over the hepatic area, the pressure within the isolated segment declined to its previous level. Intravenous injection of hexamethonium reduced not only the systemic venous pressure but also the pressure within the isolated segment of vein (Fig. 20). During all these procedures, the volume of the venous segment did not appear to change, as determined by inspection of the isolated segment. Thus, it would appear that tone in the superficial veins of the forearm was increased in the subjects with congestive heart failure and that this increase in tone was due in part to increased sympathetic nervous system activity.

General Comment

These theoretic discussions and experimental observations are compatible with an increase in tone of the smooth muscle within the wall of the systemic veins in congestive heart failure, due in part, at least, to diffuse sympathetic nervous systemic activity. There is a need to investigate this problem further to obtain additional information to understand better the mechanisms for the venous hypertension, increase in ac-

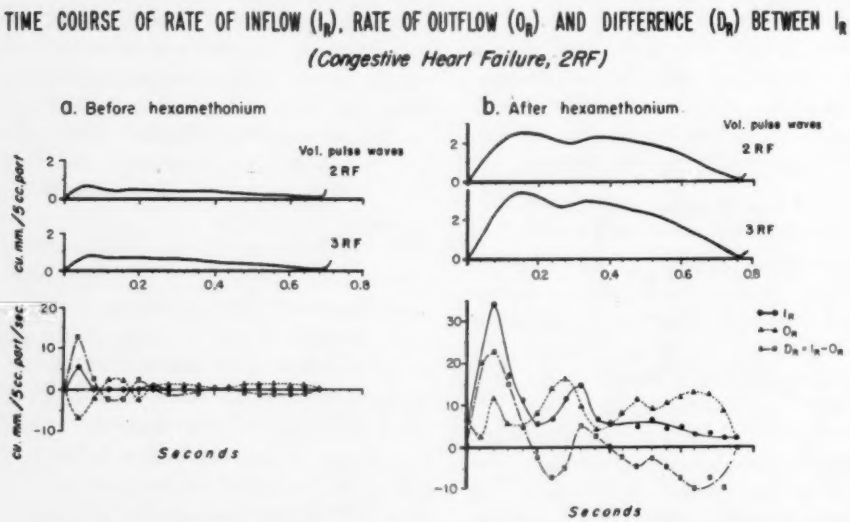

Fig. 18.—Time-course curves of the rates of inflow (I_R), outflow (O_R), and difference (D_R) between I_R and O_R for the same subject and pulse cycle shown in Figure 17. (Reproduced with permission from Burch, G. E.: A. M. A. Arch. Int. Med. 94:724 [Nov.] 1954.)

METHOD OF ISOLATION OF VENOUS SEGMENT

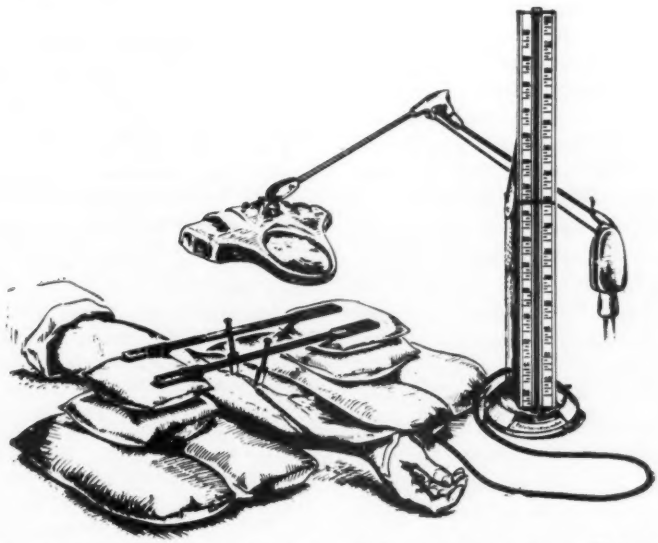

Fig. 19.—Diagram of method employed for isolating a segment of superficial vein of the forearm of a man and for following the intraluminal segmental venous pressure with the phlebomanometer. (Reproduced with permission from Burch, G. E., and Murtadha, M.: *Am. Heart J.* 51:807 [June] 1956.

TIME COURSE OF SEGMENTAL VENOUS PRESSURE

Chronic Congestive Heart Failure

(I V Hexamethonium)

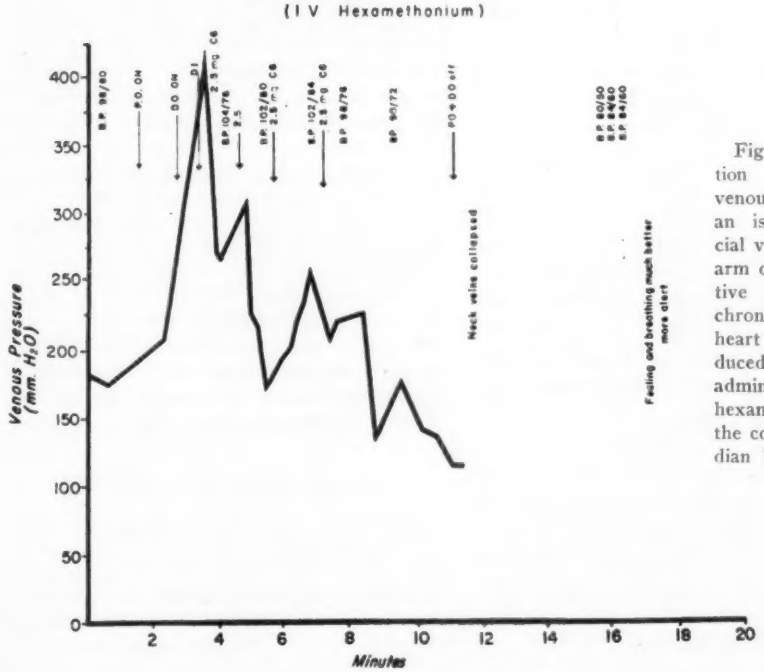

Fig. 20.—Reduction of segmental venous pressure in an isolated superficial vein of the forearm of a representative subject with chronic congestive heart failure produced by intravenous administration of hexamethonium in the contralateral median basilic vein.

tivity of the sympathetic nervous system, and associated increase in venous tone. The relationship of the venous state to the complex physiologic, chemical, and hemodynamic phenomena in congestive heart failure, as well as alterations of these phenomena by various therapeutic procedures, also require investigation. The relationship of these changes to renal function, electrolyte and water metabolism, and other cellular and organic states must be elucidated.

Studies by others[1] have provided evidence in support of increased systemic venous tone in congestive heart failure. The data of still others,† who interpreted their observations differently, can be interpreted to support increased tone of the systemic veins in congestive heart failure. These observations and their interpretations may be studied by reference to the published reports.

It does appear from experience with hexamethonium in over 100 subjects with congestive heart failure and a few experimental studies with digitalis and its derivatives that a reduction in venous pressure per se by the drugs may play a significant role in improving the clinical state of the syndrome. The direct cardiac effect of digitalis or the reduction of arterial blood pressure by hexamethonium is important, but their effect on venous pressure or venous tone, which may be direct or indirect, cannot be ignored. Finally, the increase in intensity of the pulmonic second sound and the other pulmonary and pulmonary vascular manifestations in chronic congestive heart failure may be evidence of increase in tone in the pulmonary veins in left ventricular congestive heart failure. The concepts presented for the systemic venous system most probably apply as well to the pulmonary venous system in congestive heart failure.

† References 3 and 4.

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Interpreting Medical Data

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Both acceptance and interest in formal (planned) clinical research has grown rapidly in recent years. In consequence, the number of scientific publications has increased until it is practically impossible to keep abreast of medical literature in even a single field. The physician, therefore, reads selectively of necessity. Very often it is difficult to decide which articles to study and which ones to disregard. This presentation is intended to lend assistance in making such decisions.

From current medical journals, Ross [1] analyzed 100 consecutive articles, dealing with a procedure or a type of therapy, to determine the basis upon which conclusions had been drawn. In 45% of these articles the investigators made no attempt to compare the results of the specific therapy described to those in an untreated control group, and in another 18% the control used was considered inadequate. Through this study, Ross has demonstrated the lack of a scientific attitude in current medical writing. This lack is chiefly responsible for the many controversial reports about the therapeutic effectiveness of procedures and drugs. The blame for the publication of such articles should not be placed solely on the shoulders of the authors. The editors who publish poorly controlled data and, indeed, the readers who accept such data at face value must share the responsibility.

The Role of the Art of Medicine

Every patient is different. In order for a physician to give his patients proper care he must adjust his treatments to fit their needs. The care of patients involves both art and science. In many diseases the science of medicine may be sufficient. In a self-limited illness a simple "hands-off" policy can be good therapeutics. To sell such a policy to the patient and the family requires art. Another group of diseases which might be included are those that respond readily to specific therapy. Here again, art and science cannot be completely dissociated. Some art must be part of the administration of any medication by any route. There are many patients for whom science has little to offer. Chronic progressive diseases with no specific therapy account for a large proportion of the illnesses of man. In these the art of medicine brings the greatest relief and the science is secondary to the art. Today we even perform surgery with hypnosis for anesthesia.

Subconscious or conscious influences may alter the results of an experiment. These may or may not require control and consideration prior to interpretation of experimental results. For example, if data are obtained by interpolation there is no reason to believe that one digit will be chosen more frequently than another. It is well known, however, that certain digits are selected more frequently than others. To confirm this finding, a space 10 cm. long was marked off. A slide was prepared so that a marker could be moved to any millimeter site in this space. On three different occasions one person was asked to estimate the position of the slide 100 times. The slide was moved by skips and jumps back and forth across the space until each millimeter point (from 0 to 99) was represented once on each occasion. The results are presented in Table 1.

Each of the row totals is approximately 30. This indicates the ability of the ex-

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Lilly Laboratory for Clinical Research Indianapolis General Hospital.

TABLE 1.—*Data Obtained by Interpolation* *

	0	1	2	3	4	5	6	7	8	9	Total
0	3	3	7	0	4	3	2	1	3	4	30
10	2	3	3	2	5	5	3	0	3	3	29
20	3	3	3	4	4	6	4	1	4	2	34
30	2	1	2	1	5	4	5	2	3	2	27
40	3	2	5	2	5	1	2	2	4	5	31
50	8	4	6	1	1	6	2	1	4	1	34
60	3	3	2	2	5	1	2	3	2	3	26
70	5	1	2	0	6	3	4	2	3	5	31
80	4	1	4	1	0	4	4	1	4	5	28
90	5	1	3	2	3	3	4	2	2	5	30
Total	38	22	37	15	38	36	32	15	32	35	300

* One person interpolated two digits. In this case the second digit was a guess. Each row and column should total 30 if no errors in the interpolation were made.

aminee to judge the distance in centimeters. However, the second digit of each interpolation could not be judged with any accuracy; therefore it was a guess. If chance alone controlled this guess, the number three should be reported as often as the number four. However, significantly fewer ones, threes, and sevens were reported than would be expected by chance ($x^2=25$).

In another confirmatory study, 200 people were asked to select a number with a single digit. The frequency of selection of each digit is presented in Table 2. Twenty-six

TABLE 2.—*Frequency of Selection of Digits**

Digit	No. Selecting Digit
0	4
1	4
2	8
3	32
4	14
5	33
6	24
7	52
8	15
9	14

* Two hundred persons were asked to select a number with a single digit. The frequency of selection of each digit is presented in this table.

per cent of these people selected seven, and two per cent selected zero or one. This distribution would not be expected to occur by chance ($x^2=104$). These are factors which apparently have no significance, either conscious or subconscious. No one knows how many subtle influences are part of our daily life. If such definite biases exist without apparent reason, why should we expect them to be absent when a clinical result is concerned?

In many studies one therapeutic agent is substituted for another and then comparison of past experience is made with the present result. Here the assumption is made that no change in the care of the patients occurred other than the addition of this specific therapy. The art of medicine is part of the care of all patients. No physician should minimize the importance of his art. His interest in the patient's welfare and progress, his enthusiasm or lack of enthusiasm concerning the new treatment, and the very act of obtaining data from patients, nurses, and attendants will affect the care and the responsiveness of the patient during a test period. In such studies a bias is usually produced by these factors.

Control of Bias in Clinical Research

A bias, experimentally, is any uncontrolled and/or unrecognized factor which by acting in a single direction may alter the results of the study. A brief example of a bias follows: A physician is interested in the occurrence of convulsions in the presence of fever of 104 F or higher. He finds that such seizures may occur in females twice as frequently as in males. In his study he ignores the fact that there are approximately twice as many female children in his series as there are male children and that all of the convulsions occurred in children.

The presence of any unsuspected factor is apt to lead to misinterpretation of clinical results. Such factors may occur as the result of the previous experiences of the patients or of the physician, but are most

frequently produced by the patient-physician relationship, an example of which follows: Eleven patients on the Lilly ward of the Indianapolis General Hospital professed willingness to take part in a research project. They were told that, "The purpose of this experiment is to change your sleep pattern. On alternate nights you will be given either a red capsule or a white tablet. The red capsule will help you sleep and the white medication will keep you awake." Thus, one night they would sleep well. The next night, being rested and receiving the white tablet, they would sleep poorly. On the third night, when they were tired, the red medication should help them sleep well and so forth. The medications, both of which were blanks, were given for 10 nights. Each night the patients were reminded of "the results to be expected." On the following morning, they were asked whether they had slept well or poorly. The responses are presented in Figure 1. The first patients (Group 1) indicated that they had slept well when told to do so and poorly when asked not to. These were truly cooperative persons in every sense of the word. The subjects in Group 3, however, were resistant to the suggestion that they sleep well on the red capsule and poorly on the white medication. Consciously or subconsciously they may have resented being "used for guinea pigs." If the experimentor had been a better salesman, more patients might have responded as directed; a poorer salesman might have produced even more unfavorable results. This clinician was unable to show a difference between the two placebos. If more cooperative patients had been selected a greater number of favorable results could have been obtained. The "salesmanship" of the physician is a possible source of bias in all experiments.

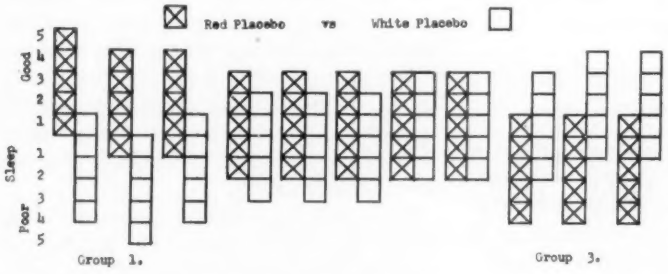

Fig. 1.—A figure presenting the number of days each of 11 patients stated they slept well or poorly after being given a placebo the night before.

Frequently, the amount of bias which would be produced must be measured and interpreted in order for the results of an experiment to have meaning. In a recent study,[2] identical capsules of three preparations (*dl*-propoxyphene [50 mg.], acetylsalicylic acid [A. S. A.]* [325 mg.] and codeine phosphate [32.5 mg.]) were given to patients with chronic pain. The drugs were given in doses of one or two capsules. All of the medications were given an equal number of times. The patients estimated the amount of pain they had experienced, and they were questioned as to the presence of nausea and vomiting, loss of appetite, constipation, diarrhea, ringing ears, dizziness, drowsiness, weakness, and well-being. In Figure 2, the frequency of positive answers is presented as the portion of the barograms above the black line; below that line is a representation of the negative responses.

In this graph we see a relatively low frequency of minor side-effects. However, the frequency increases as the dose is increased. This is presumptive evidence of a drug effect. Fortunately, in this experiment capsule *X* was a blank; *W*, *Y*, and *Z* were propoxyphene, codeine, and acetylsalicylic acid, respectively. For the interpretation of these results it is necessary to note that increasing the dose of the blank (cornstarch) from one to two capsules likewise

* Eli Lilly & Company.

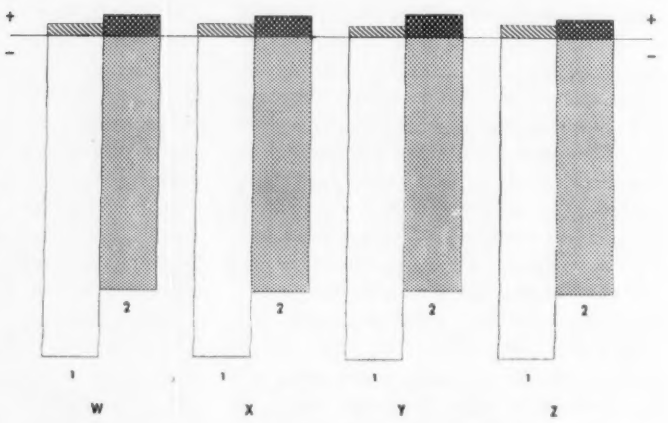

Fig. 2.—A figure presenting the frequency of undesirable effects as reported by patients receiving one or two capsules of medication.

approximately doubled the number of objectionable responses. Therefore, increasing the dose of the active drugs did not measurably increase the number of undesirable effects. This indicates the importance of the proper use of blank medications.

Indications for the Use of Placebo or Blank Medications

In research one may obtain objective or subjective data. Objective data is obtained when a measurement or count can be made which does not involve an estimation by the examinee. Measurements of blood pressure or penicillin level and counts of births or deaths are examples of objective clinical data. The pharmacologist frequently uses measurements or counts following large doses of drugs in animals. Table 3 presents data from an experiment (to be published) in which counts were made of the number of patients anesthetized within 30 seconds after intravenous injection of barbiturates. A solution of sodium chloride was included in this study and the experiment kept double-blind. The blank solution was necessary to interpret other data obtained during this experiment. For example, it was shown that the administration of any of the anesthetics significantly increased the number of ineffective electroconvulsive stimuli and prolonged the duration of apnea after stimulation.

TABLE 3.—*Data on a Group of Sixteen Patients*

Medication	Dose, Mg.	No. Patients Anesthetized
Thiopental (Pentothal)	125	7
	150	9
Thiamylal (Surital)	125	8
	150	10
Compound 22451*	15	1
	30	14
Placebo (salt solution)	5 cc.	0
	6 cc.	0

* 1-methyl-5-allyl-5-(1-methyl-2-pentynyl) barbituric acid, sodium salt.

In experiments producing objective data, blanks may not be required. Randomization of treatments is essential and when possible should be combined with the double-blind technique. In such a study neither the examinee nor the examinor knows which medication has been given. Otherwise, a completely cooperative technicion may purposely produce false results to assist the enthusiastic investigator. Investigators have committed suicide rather than retract extensive incorrect reports based on fictitious data.

At times, a study which is essentially subjective may be made partially or completely objective. When on repeated attempts we failed to measure the duration of central nervous system depression produced by various drugs, the duration was measured by examining, at hourly intervals, patients who were given larger than usual doses of hypnotics.[3] The drugs were given at ran-

TABLE 4.—*Central Nervous System Depression in Ten Patients After Oral Doses of Ethinamate or Chloral Alcoholate*

		Sleepy		Lethargic		Stuporous		Comatose		Row Totals	
	Dose, Gm.	Ethinamate	Chloral Alcoholate	Ethinamate	Chloral Alcoholate	Ethinamate	Chloral Alcoholate	Ethinamate	Chloral Alcoholate	Ethinamate	Chloral Alcoholate
No. patients demonstrating each intensity of effect	1.0	9	8	4	3	0	0	0	0	13	11
	1.5	10	10	9	5	3	0	1	0	23	15
	2.0	10	10	10	5	3	3	2	1	25	19
	Total	29	28	23	13	6	3	3	1	61	45
No. hours depression of given intensity (or greater) persisted (totals for 10 patients)	1.0	40	35	15	11	0	0	0	0	55	46
	1.5	56	45	36	12	6	0	3	0	101	57
	2.0	62	54	46	28	13	14	6	2	127	98
	Total	158	134	97	51	19	14	9	2	283	201

dom on a double-blind basis. Since comparison of equally effective doses was necessary in order to compare properly duration, potency measurements were also made. This study (Table 4) indicated that ethinamate (Valmid)† was half again as effective as chloral alcoholate (the pharmacological equivalent of chloral hydrate). Since the relative potency of these two drugs might not remain the same if smaller doses were given, a study with subjective measurements was also undertaken. The data, reported in Table 5, confirm the conclusions that ethinamate is more potent than chloral alcoholate. The same relationship was observed when the duration of the effect of the drugs was determined. However, doses which produced the same intensity of response had effects of equal duration. The use of placebos was essential to the subjective, but not to the objective, part of this study.

There are some experiments which can never be made objective. Pain is dependent upon stimuli and interpretation. The interpretation is always subjective. In the comparison of propoxyphene, codeine, and acetylsalicylic acid previously mentioned,[2] estimates of pain intensity reported by the patients were essentially the same no matter which drug or dose was given. However, when one capsule of placebo was given instead of one of the analgesic capsules, the estimate of pain increased significantly, and a marked increase in the estimate of pain

† Eli Lilly & Company.

TABLE 5.—*Patients' Estimates of the Results of Administration of 250 or 500 Mg. of Chloral Alcoholate or Ethinamate at Bedtime*

		Quality of Sleep			Quantity of Sleep			
Medication	Dose, Mg.	Good	Intermediate	Poor	Onset, Min.	Duration, Hr.	Interruptions	Dream
Placebo	250	10	5	4	64	7.4	36	6
Chloral	250	15	2	2	55	7.6	38	0
Ethinamate	250	17	1	1	44	7.7	16	0
Placebo	500	21	4	7	97	6.9	69	8
Chloral	500	22	3	7	77	7.7	60	9
Ethinamate	500	28	2	2	58	7.7	34	8

Symptoms and Sensations Observed on Awakening

	250 Mg.			500 Mg.		
	Placebo	Chloral	Ethinamate	Placebo	Chloral	Ethinamate
Mental obtundity	3	6	2	8	7	7
Weakness	2	0	0	1	0	0
Fatigue	6	8	3	1	9	7
Sweating	2	1	3	0	1	1
Headache	2	8	3	5	6	3
Nausea and heartburn	0	2	1	3	2	2
Abdominal cramps	1	1	0	2	2	1
Malaise or pain	2	2	1	6	2	2
Dizziness	0	3	1	3	6	4
Restlessness	1	2	0	11	7	4
Nervousness	0	0	1	0	0	0
Anxiety	1	0	1	2	4	0
Totals	20	33	16	42	46	31

was reported when two blank capsules were substituted for two capsules of analgesic. To interpret these results one may assume that a sudden change produced by the administration of a blank may be interpreted by the patient as increase in pain. The extent of the increase is dependent upon the difference between the analgesic effect and the effect of the blank. The change is greater when two capsules of placebo are substituted for two of analgesic than when one is substituted for one.

In the experiment with analgesics, if the blank had not been given, the following conclusions would be reached. First, the undesirable effects increase when the dose of analgesic is increased; second, increasing the dose of the analgesic does not change the estimates of pain. The use of the blank makes it possible for the results to be interpreted as follows. First, no significant undesirable effects were produced by the analgesics; second, significantly more analgesia was produced when the doses of acetylsalicylic acid, codeine, and propoxyphene were doubled (Fig. 3). Of course, all experimental data must be interpreted clinically. Statistics support clinical interpretation and should not replace judgment. This interpretation of the above experiment, from a clinical standpoint, is logical and therefore becomes acceptable.

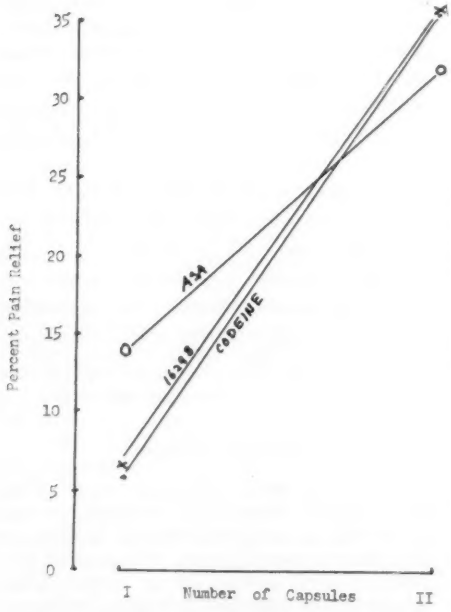

Fig. 3.—A figure presenting the per cent pain relief obtained by the 14 patients included in Table 1. The per cent pain relief was obtained from the scoring data by the formula

$$\frac{\text{Placebo score} - \text{drug score}}{\text{placebo score}} \times 100.$$

Conclusions

These considerations concerning biases and methods of testing new therapeutic ideas indicate that when we read medical writing or write for medical reading we must ask of ourselves "Have sources of bias been controlled in this study?" If the controls are not adequate, the conclusions are no better than a guess. Let us look at the controls.

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Severe Osteomalacia Associated with Occult Steatorrhea Due to Nontropical Sprue

Report of Five Cases

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Osteomalacia is a metabolic disturbance of bone characterized by insufficient deposition of calcium salts into bone matrix. Patients with this disease often complain of muscular weakness and skeletal pain. They may exhibit deformities of bones, and not infrequently they have hypocalcemic tetany. The concentrations of either the serum calcium or the serum inorganic phosphorus or both are found to be low; the level of serum alkaline phosphatase is frequently elevated.[1] As the disease progresses, roentgenograms may reveal diminished density of bones, particularly of the long bones of the extremities and the vertebrae. Linear zones of decreased density, first described by Looser[2] and later termed "pseudofractures" by Milkman,[3] may become evident. These seams of decalcified osteoid tissue tend to be symmetrically located and are most commonly found at the axillary edge of the scapulae and in the neck of the femurs, the pubic and ischial rami, and the ribs.

One of the commonest causes of osteomalacia in this country is poor absorption of calcium from the gastrointestinal tract secondary to prolonged untreated steatorrhea. Nontropical sprue (idiopathic steatorrhea) is a frequent and important cause of steatorrhea and must always be considered when the cause of osteomalacia is obscure. As others * have pointed out, nontropical sprue may not present with the classic textbook picture of frequent, copious, fatty, foul-smelling stools. Sometimes the patient will have normal bowel habits, and the secondary manifestation of osteomalacia may completely dominate the clinical picture.

The clinical and laboratory data of five patients with osteomalacia secondary to occult steatorrhea will be reported. In each case the diagnosis of nontropical sprue was initially overlooked because the presenting complaints of each patient involved the musculoskeletal system, and gastrointestinal symptoms usually were not associated.

Report of Cases

CASE 1.—A 40-year-old woman came to the Mayo Clinic in March, 1937, complaining of pain in the left hip associated with pain in both feet and ankles on weight bearing. The pain had been present about 15 months. For six months she had had progressive difficulty on walking because of the pain, and her feet and legs tended to swell if she stood or walked excessively. She had lost 12 lb. during the past year. A diagnosis of anemia had been made elsewhere six years previously. Subsequently, intermittent soreness of the mouth and tongue had developed. During the nine months preceding her examination at the clinic, the patient had received 14 intramuscular injections of crude liver extract, presumably for the anemia and sore mouth. Ordinarily she had one bowel movement per day, but on infrequent occasions when her "blood was down" she remembered having had two or three soft stools per day.

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* References 4 and 5.

On physical examination at the clinic the patient weighed 80 lb., and the blood pressure measured 130 mm. of mercury systolic and 85 mm. diastolic. She was extremely weak and had generalized muscular tenderness. The borders of the tongue were smooth. There was slight pitting edema of both legs. Moderate tenderness to percussion was present over the sacroiliac joints, and the straight-leg-raising test on each side produced pain in the region of both these joints. Complete neurologic examination revealed no abnormalities.

Roentgenograms of the lumbosacral region, pelvis, and hips were normal. The value for hemoglobin was 10.4 gm. per 100 cc. of blood, and the erythrocyte count was 4,250,000 per cubic millimeter. The blood smear revealed hypochromic anemia with only an occasional macrocyte. Gastric analysis (Töpfer's method) yielded 8 units of free hydrochloric acid.

The anemia was considered to be nutritional in origin, but the cause of the musculoskeletal symptoms remained obscure. A diet high in vitamins was prescribed along with supplemental doses of ferrous sulfate by mouth and crude liver extract given parenterally.

The patient returned in July, 1940, complaining of aching and stiffness in both hips, the back, and throughout the chest. She was very weak and tended to stagger when she walked. A sacroiliac support gave her considerable relief. She stated that for one year after her last visit she had felt well and was able to get about without difficulty; her musculoskeletal symptoms then recurred, and disability increased progressively. Seven months prior to her return to the clinic she experienced frequent carpal spasms. Evidence of a fracture of the pelvis was reported in the roentgenograms taken one month prior to her return. Bowel habits were unchanged.

Physical examination on this visit revealed moderate limitation of all motions of the lumbar portion of the spinal column and abduction of both hips. There was no pubic or ischial tenderness. A roentgenogram of the thorax revealed multiple symmetrical pseudofractures of the ribs. Roentgenograms of the pelvis showed considerable demineralization of bone with bilateral pseudofractures through the pubic and ischial rami. There were also pseudofractures of both scapulae, the metatarsals of each foot, the lower portion of each fibula, each radius and ulna, and each second metacarpal. The value for hemoglobin was 10.8 gm. per 100 cc., the erythrocyte count was 4,750,000 per cubic millimeter, and examination of the blood smear revealed macrocytosis. On two occasions, tests disclosed values for serum calcium of 5.8 and 5.9 mg. per 100 cc.; for serum inorganic phosphorus, of 2.9 and 3.1 mg. per 100 cc., and for serum alkaline phosphatase, of 7.1 and 5.2 Bodansky units per 100 cc.

The patient was advised to drink at least 1 qt. (1 liter) of milk a day and to take 6 teaspoons (30 ml.) of calcium lactate dissolved in water and 3 fluidrachms (12 cc.) of cod liver oil every day. She also was advised to continue to take the parenteral injections of crude liver extract twice a month. Five months later she reported remarkable symptomatic improvement and that she was relatively free of pain and was doing most of her own housework.

The patient returned in July, 1941, at which time she was feeling well and had no specific complaints. Physical examination was essentially negative. Roentgenograms again showed some demineralization of bone with old pseudofractures of the pubic rami, ribs, and left third metatarsal. The value for hemoglobin was 12.3 gm. per 100 cc., the erythrocyte count was 4,220,000 per cubic millimeter, and the blood smear was normal. Values for serum calcium were 8.3 mg., for serum inorganic phosphorus 2.9 mg., and for alkaline phosphatase 3.9 Bodansky units per 100 cc. The patient was advised to follow the same regimen outlined one year previously.

She returned in September, 1942, with no essential change in physical condition. She had noted some bloating during the past year, which she attributed to drinking milk. In addition she noted recurrent episodes of watery diarrhea occurring three or four times a month and lasting about one day. A diagnosis of nontropical sprue was considered, but the patient was unable to stay for confirmatory studies. Continued use of the same regimen was advised.

She returned in November, 1948, because she had lost 20 lb. during the previous year, and her feet and ankles had been swollen for several months. Episodes of watery diarrhea lasting one to five days had caused her much distress during the past year. The stools were not described as bulky, fatty, or frothy.

On physical examination the patient weighed 77 lb. She appeared thin and malnourished, with a dry skin and a distended abdomen. There was moderate bilateral pretibial edema. A roentgenogram of the chest revealed old fractures of the fifth and sixth ribs in the left posterior axillary line. Roentgenologic examination of the small intestine revealed a deficiency pattern compatible with a diagnosis of nontropical sprue. The total amount of fat in a stool specimen collected over 24 hours was 45.4 gm. The value for hemoglobin was 11.5 gm. per 100 cc., and the erythrocyte count was 4,310,000 per cubic millimeter. Examination of the blood smear revealed mild macrocytosis. A diagnosis of nontropical sprue was made, and the patient was advised to continue the regimen previously outlined, with the addition of one multiple-vitamin capsule daily and a diet low in fat.[6]

The patient returned in September, 1955, complaining of weakness and numbness of the hands and feet. During the past six months she had had recurrent episodes of diarrhea, with five or six stools per day. The stools were now more formed and tended to float. There was no recent history of carpopedal spasm.

The physical examination revealed an essentially unchanged condition except for a positive Chvostek sign. The findings in the peripheral blood were the same too. A roentgenogram of the small intestine again showed a deficiency pattern. The level for serum calcium was 8.3 mg., and that for serum alkaline phosphatase, 25.5 King-Armstrong units per 100 cc. The diagnosis of nontropical sprue was confirmed, and the patient was urged to continue the previous regimen and to take additional calcium and vitamins by mouth each day, particularly vitamin D in the form of cod liver oil, and parenteral injections of liver extract twice a month.

CASE 2.—A 55-year-old housewife was first seen at the clinic in August, 1949, complaining of pain and stiffness in both knees of four years' duration. A diagnosis of menopausal arthritis had been made elsewhere. The pain was not affected by changes in weather, and she had noted minimal stiffness in the knees in the morning. Her chief difficulty occurred when she arose from a sitting position and when she walked upstairs; she also stated that her back tired easily. For some time she had resorted to the use of a cane in order to minimize pain and weakness of the knees in walking. A decrease of 12 lb. in weight during the preceding year was attributed by the patient to inadequate intake of food. Her only gastrointestinal complaint was recurrent nausea following ingestion of fatty foods. She denied having any unusual bowel symptoms except that she recalled having had a bout of diarrhea approximately 20 years previously which lasted several months. She stated that she had one or two stools per day, which were likely to be mushy and light-colored and sometimes floated.

On examination her weight was recorded as 100 lb. and the blood pressure as 96 mm. of mercury systolic and 60 mm. diastolic. A firm adenoma in the left lobe of the thyroid, measuring 6 cm. in diameter, displaced the trachea to the right. The patient appeared to be euthyroid. Examination of the joints gave negative results except for small Heberden's nodes. There was moderate weakness of the quadriceps and hamstring muscles, more marked in the left than the right leg. The Trousseau sign was positive in one minute.

Roentgenograms of both knees and the thoracolumbar vertebrae revealed marked demineralization of bone. The concentration of hemoglobin was 10.8 gm. per 100 cc., the erythrocyte count was 2,530,000 per cubic millimeter, and examination of the blood smear revealed a pernicious anemia type of picture, with macrocytosis and mild polychromasia. The values per 100 cc. for serum calcium were 6.4 and 7.7 mg.; for serum inorganic phosphorus, 3.4 and 3.6 mg.; for alkaline phosphatase, 7.0 Bodansky units; for serum carotene, 18.0 I. U.; for serum albumin, 3.6 gm., and for serum globulin, 2.4 gm. The prothrombin time was 20 seconds (normal, 17 to 19 seconds). The glucose tolerance test yielded a flat type of curve. Stools collected over 24 hours contained 29.8 gm. of fat and 3.7 gm. of nitrogen; fat constituted 44.9% of the dry weight of the stool. Roentgenologic examination of the small intestine showed a deficiency pattern characteristic of nontropical sprue.

A diagnosis of nontropical sprue with secondary osteomalacia was made, and a program consisting of a high-carbohydrate, high-protein, low-fat diet was started, with intramuscular injections of crude liver extract four times a week initially and at less frequent intervals later, calcium lactate by mouth daily, and 50,000 units of calciferol (crystalline vitamin D_2) daily.

The patient returned to the clinic in June, 1950, at which time she felt much stronger. Pain was no longer present in the bones and joints. On this occasion the serum calcium measured 8.2 mg.; serum inorganic phosphorus, 4.7 mg., and alkaline phosphatase, 4.7 Bodansky units per 100 cc. A 48-hour collection of stools contained an average of 13.1 gm. of fat per day; this constituted 66.4% of the dry weight of the stool. The value for hemoglobin was 11.5 gm. per 100 cc.; the erythrocyte count, 4,210,000 per cubic millimeter, and the blood smear, normal.

The patient returned in April, 1953, complaining for the first time of diarrhea with foul-smelling watery stools, loss of weight, and edema of the ankles. One year previously she had omitted the prescribed diet and medication for six weeks; frank symptoms of sprue developed and persisted even after she resumed in part the regimen originally outlined. The serum calcium now measured 6.6 mg.; the serum inorganic phosphorus, 3.9 mg.; the alkaline phosphatase, 7.4 Bodansky units; serum albumin, 3.0 gm., and globulin, 1.6 gm. per 100 cc. The prothrombin time was 44 seconds. Fat comprised 47.9% of the dry weight of the stool. The patient was hospitalized and started on the treatment program outlined previously with the addition of the oral administration of a synthetic preparation having vitamin-K-like activity. A gradual remission of symptoms occurred, and the patient was dismissed much improved.

On a return visit in January, 1955, she complained of loose, sometimes foamy, stools which were more frequent after ingestion of fat and occurred mainly at night. These symptoms had been present for the preceding two months. The

patient had not been following her treatment regimen strictly for several months. Except for these symptoms, and tiredness when she had been on her feet for prolonged periods, she had felt well. Examination of the blood disclosed 9.8 gm. of hemoglobin per 100 cc., 3,810,000 erythrocytes per cubic millimeter, and mild hypochromasia, with scattered macrocytes. The serum contained 7.5 mg. of calcium per 100 cc., 4.6 mg. of inorganic phosphorus per 100 cc., 34.0 King-Armstrong units of alkaline phosphatase, 2.82 gm. of albumin per 100 cc., and 2.20 gm. of globulin per 100 cc. The prothrombin time was 22 seconds. On dismissal she was advised to follow a diet low in fat and high in carbohydrate and protein. The patient was also advised to take 100,000 units of vitamin D daily for one month and 50,000 units daily thereafter. She was given 3 teaspooons (15 ml.) of calcium lactate dissolved in water twice daily. In addition, 1 cc. of liver extract to be given intramuscularly twice each week was prescribed.

CASE 3.—A 42-year-old housewife entered the clinic in May, 1950, with the chief complaint of an aching pain low in the back of four months' duration. This pain was aggravated by bending, lifting, sneezing, and by getting out of bed. Shortly after the onset of this pain, the patient noticed pain on each side of her chest which was accentuated by deep inspiration and by rolling over in bed. The pain in the back and lateral chest wall became gradually but progressively severer.

The patient considered her general health to be good. A subtotal hysterectomy for uterine procidentia had been performed elsewhere about one year previously. Since this operation she had had a few attacks of diarrhea, which lasted one or two days each. She admitted to some flatulence and bloating but usually had one formed stool per day which was not fatty or frothy and contained no undigested food particles. There was no history of loss of weight.

Physical examination revealed moderate limitation of posterior and lateral movements of the spinal column and marked bilateral tenderness of the sides of the thoracic cage. Expansion of the chest was good, but there was some pain on deep inspiration.

A roentgenogram of the chest showed nothing of significance. Roentgenograms of the lumbar portion of the spinal column revealed generalized demineralization, with some ballooning of the intervertebral spaces (the so-called codfish vertebrae). Roentgenograms of the pancreatic area revealed no evidence of calcification. Roentgenograms of the skull showed marked demineralization of bone, and those of the teeth revealed intact lamina dura.

The following pertinent laboratory findings were reported: 11.3 gm. of hemoglobin per 100 cc. of blood; 4,490,000 erythrocytes per cubic millimeter; 6.7 and 7.3 mg. of serum calcium per 100 cc; 2.5 and 2.6 mg. of serum inorganic phosphorus per 100 cc. and 9.9 and 12.1 Bodansky units of alkaline phosphatase. There was 26.0 gm. of fat per day in a 48-hour collection of stools; this constituted 57.2% of the dry weight of the stool.

On the basis of these findings a diagnosis of nontropical sprue with secondary osteomalacia was made. The patient was instructed to take a diet high in carbohydrate and protein and low in fat. Also prescribed for her were intramuscular injections of concentrated liver extract, a vitamin-K-like substance by mouth twice weekly, 50,000 units of vitamin D by mouth daily, and 2 teaspoons (10 ml.) of calcium lactate dissolved in water by mouth three times daily.

The patient returned in July, 1953, with the main complaint of general fatigue. She had had no medication for the preceding nine months. She was free from bone pain, but she now had occasional diarrhea, with bulky stools. Physical examination gave essentially negative results. Roentgenograms of the lumbar portion of the spinal column showed no appreciable change from previous findings. Laboratory tests revealed 8.9 mg. of serum calcium per 100 cc., 3.7 mg. of serum inorganic phosphorus per 100 cc., and 3.8 Bodansky units of alkaline phosphatase. A 24-hour-stool specimen contained 14.5 gm. of fat, and fat constituted 41.5% of the dry weight. She was advised to resume the regimen originally outlined for her.

CASE 4.—A 71-year-old housewife came to the clinic in September, 1954, complaining of aching pain in the shoulders, back, and hips. Early in 1952, pain first developed beneath the right scapula, which her local physician ascribed to rheumatism. This did not improve, so she sought help from chiropractic manipulations. It was her impression, however, that following this treatment aching pain developed in the shoulders and thorax. During the next year she noted the onset of pain in the hips, swelling of both ankles, and increasing difficulty in walking. Because of pain and stiffness low in the back and in the hips it was difficult for her to get out of bed. Overactivity accentuated the pain; when sitting quietly, she had no pain. Despite a good appetite, the patient had lost about 15 lb. since the onset of her illness. Bowel habits were normal. She had one or two formed stools per day, which were of normal color and contained no noticeable undigested particles of food or fat. A diagnosis of pernicious anemia had been made elsewhere some 15 years previously, and for this, injections of crude liver and later of cyanocobalamin (vitamin B_{12}) had been given at regular intervals ever since.

Physical examination revealed a frail woman who weighed 82 lb. and used a wheel chair because of slow painful walking. She had pain and

tenderness over the ribs on both sides, which spread to the back and up the thoracic vertebrae. Motion of the hips was markedly limited and painful bilaterally.

Roentgenograms revealed decreased density of the vertebrae, the pelvis, and the hips, with fractures of the eighth and ninth ribs on the right, pseudofractures of the inferior pubic rami, and a possible fracture of the left superior pubic ramus. Roentgenograms of the pancreatic region revealed no evidence of calcification. Roentgenologic examination of the small intestine gave negative results.

Results of the routine laboratory tests were normal. The values per 100 cc. for serum calcium were 7.9 and 7.7 mg.; for serum inorganic phosphorus, 1.7 and 2.0 mg., and for alkaline phosphatase, 67.5 King-Armstrong units. A 72-hour collection of stools contained an average of 49.3 gm. of fat and 6.6 gm. of nitrogen per day. Fat comprised 52.9% of the dry weight of the stool.

A diagnosis of nontropical sprue with secondary osteomalacia was made. Further detailed questioning of the patient elicited a history of fatty diarrhea for seven years prior to 1922. At that time she had as many as seven stools per day, but the diarrhea disappeared when she became pregnant and did not return.

The treatment program consisted of 200,000 units of calciferol, 4 mg. of vitamin-K-like substance, and 3 teaspoons of calcium lactate dissolved in water by mouth daily. She was instructed in a diet high in protein and containing approximately 75 gm. of fat per day and was told to continue with the injections of cyanocobalamin as before.

Six months later (March, 1955) the patient exhibited remarkable clinical improvement. She had discarded the wheel chair in December, 1954, and now had no complaints except for fatigue in the shoulder girdle after excessive use of both arms. The value for serum calcium on this visit was 9.4 mg.; for serum inorganic phosphorus, 3.3 mg., and for alkaline phosphatase, 13.6 King-Armstrong units per 100 cc. Stool examination showed 56.3 gm. of fat in the specimen, and this fat constituted 59.9% of the dry weight of the stool.

Case 5.—A 43-year-old housewife came to the clinic in October, 1954, with a history of progressive pain and stiffness in both legs and difficulty in walking of two years' duration. The disability began rather suddenly, and an extensive medical examination elsewhere resulted in a diagnosis of fibrositis and nervousness. The patient had lost approximately 30 lb. since the onset of her illness. She gave no history of diarrhea except for short and infrequent spells of "intestinal flu" when other members of the family had a similar complaint. She usually had two stools per day, sometimes three, and on rare occasions none at all; the stools were usually formed but sometimes were soft and watery. She remembered having been wakened from sleep on a few occasions by the need to defecate. She gave no history of flatulence or intolerance to food.

Physical examination revealed very dry skin. The patient walked with the aid of two canes and had a rolling, wide-based gait. When walking without her canes, she would help move her legs with her hands. There was marked weakness of the abductors and flexors of the hip. Quick motions of either hip were painful, and external rotation of the hips was moderately limited because of pain.

Roentgenologic examination of the spinal column and both femurs revealed diffuse demineralization of bone, with pseudofractures of the neck of each femur. Roentgenologic examination of the small intestine showed a pattern consistent with a low-grade deficiency state such as is seen in nontropical sprue. The value for hemoglobin was 11.2 gm. per 100 cc., and the blood smear showed mild hypochromasia and anisocytosis, with a fair number of macrocytes. The values for serum calcium were 7.9 and 8.4 mg. per 100 cc. on separate determinations; for serum inorganic phosphorus, 2.7 and 2.4 mg. per 100 cc.; for alkaline phosphatase, 72.0 King-Armstrong units; for serum albumin, 3.73 gm. per 100 cc., and for serum globulin, 1.89 gm. per 100 cc. The prothrombin time was 20 seconds. Stools collected for 48 hours while the patient was taking a diet with a daily content of 100 gm. of fat contained 10.9 gm. of fat per day. Fat constituted 36.6% of the dry weight of the stool.

A diagnosis of nontropical sprue with secondary osteomalacia was made. The patient was started on a regimen of calcium lactate, dissolved in water, vitamins D and K by mouth, and parenteral injections of liver extract. She was instructed concerning a full sprue diet.[8] A program of physical therapy was outlined for use at home.

The patient was markedly improved when she returned in April, 1955. She stated that shortly after being dismissed in December, 1954, she began to use only one cane, and after January, 1955, she no longer needed assistance in walking. She had noted no bowel symptoms except for a tendency to be constipated. The value for hemoglobin now was 10.5 gm. per 100 cc., and the blood smear showed some hypochromasia but no macrocytosis. The level of serum calcium was 9.2 mg. per 100 cc.; of serum inorganic phosphorus, 4.1 mg. per 100 cc., and of alkaline phosphatase, 8.2 King-Armstrong units.

Comment

The cases reviewed serve to emphasize the fact that nontropical sprue may exist

with minimal gastrointestinal symptoms but with the severe secondary manifestations of osteomalacia. Each of these patients came to the clinic complaining of skeletal pain, usually involving the back or lower extremities. Stiffness and weakness were associated, and the pain was aggravated by movement of the affected part, by weight-bearing, or by lifting. Three of the five patients (Cases 2, 4, and 5) had enough difficulty walking so that a cane or wheel chair was needed to assist them in getting about. These same patients had received a diagnosis of rheumatism or fibrositis previously in an effort to account for their skeletal pain and weakness. Three of our patients also complained of pain in the thorax.

In all five cases the serum calcium was below normal level initially; in three cases the serum inorganic phosphorus was below normal level, and in all five cases the level of serum alkaline phosphatase was elevated initially. Roentgenologic evidence of demineralization of bone, especially in the spinal column and lower extremities, was found in each case. Typical pseudofractures of the pubic rami or femoral necks were present in Cases 1, 4, and 5.

Significant gastrointestinal symptoms were elicited, if at all, only after the most detailed questioning in a search for the cause of the established osteomalacia. After such interrogation, two of the patients were able to recall an episode of prolonged diarrhea 20 or more years prior to their first admission to the clinic. The remaining patients had had only occasional and transient episodes of diarrhea, one of whom regarded them as "intestinal flu." All but one of the patients (Case 3) had lost from 12 to 30 lb. Our patients were all women, the youngest of whom was 40 years of age when first examined. The pertinent clinical and laboratory data are summarized in the Table.

A medical program for the treatment of nontropical sprue was instituted in each case. This included a diet low in fat (approximately 45 to 75 gm.) but high in protein, carbohydrate, and Calories.[6] The patients had additional calcium, as calcium lactate by mouth, 50,000 to 200,000 units of calciferol daily by mouth, 4 mg. of a synthetic vitamin-K-like substance by mouth each day or twice a week depending on the severity of the steatorrhea, crude liver extract, and each day a multiple-vitamin capsule. All of the patients had marked remission of their osteomalacic symptoms. The symptoms improved, and the values for calcium, phosphorus, and alkaline phosphatase in the blood tended to return to normal as long as the patients followed the program outlined for them. In the cases of pseudofractures there was complete healing of these lesions after adequate treatment had been carried out. However, roentgenologic evidence of bone demineralization persisted to some degree in all cases studied.

Many reports have appeared in the literature on osteomalacia complicating the sprue syndrome. In the early descriptions of nontropical sprue by Holmes and Starr [7] and Thaysen,[8] reference is made to patients who presented with fatty diarrhea, progressive loss of weight, and bone pains in the vicinity of the hips, knees, or ankles. Roentgenograms showed the joints to be normal, but the bones were markedly demineralized. Since these early reports, other cases of nontropical sprue with secondary osteomalacia have appeared.† In an analysis of 85 patients with sprue in which the serum calcium and phosphorus were determined,[11] 40 (47%) had chemical osteomalacia, that is, low or normal levels of serum calcium or phosphorus or both. Roentgenographic evidence of bone disease was demonstrable in 22 cases (26%) of this series.

Because of the frequency with which osteomalacia develops in patients with nontropical sprue, we prescribe for all of them a high calcium intake and extra amounts of vitamin D as a preventive measure even when no clinical or laboratory evidence of osteomalacia has been demonstrated. In a general way the amount of calcium and vitamin D prescribed depends on the degree

† References 1, 9, and 10.

Symptoms and Findings of Diagnostic Importance

Case	Age (Yr.) & Sex	Presenting Complaint	Serum*			Fat Content of Stool		Roentgenographic Findings
			Calcium, Mg./100 Cc.	Inorganic Phosphorus, Mg./100 Cc.	Phosphatase, Units	Gm./Day	Per Cent Dry Weight	
1	40 F	Pain in the lower extremities on weight-bearing; difficulty walking	5.8 5.9	2.9 3.1	7.1† 5.2†	45.4	....	1. Extensive demineralization of entire skeleton, with pseudofractures of ribs, pubic rami, and scapulae 2. Deficiency pattern in small intestine
2	55 F	Pain and stiffness of the knees; difficulty walking	6.4 7.7	3.4 3.6	7.0†	29.8	44.9	1. Marked demineralization of thoracolumbar vertebrae and femurs 2. Deficiency pattern in small intestine
3	42 F	Persistent pain in back and chest aggravated by movement	6.7 7.3	2.5 2.6	9.9† 12.1†	26	57.2	1. Demineralization of lumbar spine and skull 2. No x-rays of small intestine
4	71 F	Aching pain in shoulders, back, and hips; increasing difficulty walking	7.9 7.7	1.7 2.0	67.5‡	49.3	52.9	1. Demineralization of spine, pelvis, and femurs, with pseudofractures of ribs and pubic rami 2. Small bowel normal
5	43 F	Pain and stiffness in both legs; difficulty walking	7.9 8.4	2.7 2.4	72.0‡	10.9	36.6	1. Diffuse demineralization of spine and femurs, with pseudofractures of both femurs 2. Deficiency pattern in small bowel

* Results are for first two tests performed.
† Bodansky units (normal range <5 units).
‡ King-Armstrong units (normal range <14 units).

of steatorrhea present. In mild cases sufficient calcium may be obtained from milk in the diet if this food is well tolerated by the patient. Supplementary calcium may be administered as calcium lactate powder, 3 to 9 teaspoons (15 to 45 ml.) per day, dissolved in boiling water which is ingested after cooling. The dose of vitamin D necessary either for the prevention of osteomalacia or its treatment is not easy to determine and seems to vary a good deal from one patient to another. In both circumstances the dosage may require adjustment based on follow-up clinical and laboratory studies of the patients. For prophylaxis we have frequently given as high as 2000 to 5000 units per day. Osteomalacia has been shown to develop in patients with steatorrhea while they were receiving 1500 units of vitamin D and 2 gm. of calcium lactate per day.[12] For severe osteomalacia or for osteomalacia in patients resistant to orally administered vitamin D, doses as high as 300,000 units per day are sometimes necessary. These large doses can usually be reduced as the patient responds to treatment, and maintenance doses of 25,000 to 50,000 units per day may eventually be found to control the condition satisfactorily. Theoretically, water-miscible preparations of vitamin D should be more readily absorbed from the bowel of patients with nontropical sprue than oily ones, as is the case with vitamin A.[13] In practice, however, we have found oily preparations to be less expensive and more conveniently administered, advantages which have seemed to outweigh the disadvantage of less complete absorption. It is our custom to advise periodic examinations of the serum calcium at intervals of three to six months in order to detect evidences of hypervitaminosis D, especially in patients taking large doses of this vitamin. Thus far we have not encountered hypercalcemia or other evidences of vitamin D intoxication in patients with nontropical sprue who have been receiving the vitamin in prophylactic or therapeutic doses.

Relatively few cases have been reported in which the osteomalacic symptoms are the predominant and presenting complaint of patients with occult steatorrhea. In 1935, Langmead[14] reported a case of progressive pain and stiffness in the lumbar region due to osteomalacia; although this patient always tended to be constipated, examination of the fat content of the stool revealed steatorrhea. Short[15] reported a case of steatorrhea without diarrhea in which there was a six-year history of progressive skeletal changes due to osteomalacia. Anderson[4] presented a case in which the gastrointestinal symptoms were minimal but the secondary manifestations were severe and included multiple pseudofractures. Strang[10] cited a case in which severe pain in the hips and low in the back was due to decalcified bone, a pseudofracture of one femur, and a complete fracture of the other femur. This patient had no gastrointestinal symptoms, but later studies revealed occult steatorrhea. Cameron and associates[5] found steatorrhea in eight adults, none of whom had symptoms referable to the bowel. Two of these eight had skeletal pain as their chief complaint. Pilcher[16] reported the case of a woman with bone pain due to osteomalacia who initially gave a history of perfectly normal bowel habits. However, on close questioning she admitted passing four or five bulky unformed stools a day for as long as she could remember and had come to regard this as normal.

The precise mechanism by which the sprue syndrome produces a negative calcium balance with subsequent osteomalacia is unknown. It is well documented[17] that there is an excessive loss of calcium in the feces of patients with steatorrhea. This loss of calcium has been thought to be due to the increased amounts of fecal fat passed by these patients. With the large amounts of unabsorbed fat, much of the fat-soluble vitamins, including vitamin D, is lost in the feces; vitamin D deficiency in turn leads to diminished intestinal absorption of ingested calcium. Hypovitaminosis D is very likely an important factor in the patho-

genesis of osteomalacia due to steatorrhea,‡ and this hypothesis has support in the facts that (1) vitamin A and K deficiencies are frequently seen in cases of steatorrhea and (2) the administration of vitamin D significantly increases the absorption of calcium in patients with sprue.[19] In addition to vitamin D deficiency, it is also likely that small amounts of calcium remain unabsorbed because of a combination with the excessive fatty acids in the bowel to form insoluble soaps.[20] Finally, while a high content of fat in the stool is usually accompanied by a high content of calcium, this correlation is far from exact and may be merely a reflection of the severity of the sprue syndrome.[17] Thus it is probable that large amounts of calcium are lost in idiopathic steatorrhea due to a malabsorption of calcium per se because of the generally poor absorptive powers of the small intestine in this disease.

Summary

The clinical and laboratory findings in five cases of osteomalacia secondary to an occult steatorrhea are presented. In each case the patient sought medical aid because of severe disabling skeletal pain with few or no symptoms referable to the gastrointestinal tract. The diagnosis of nontropical sprue was made only after a careful search for the underlying cause of the osteomalacia.

‡ References 12 and 18.

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Natural History of Glomerular Nephritis

A Report of Patients Treated From Ten to Twenty-Five Years After the Acute Stage

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There is almost complete unanimity of opinion that chronic glomerular nephritis is the outcome of an acute phase which fails to heal completely. When the acute attack is over, which usually occurs within a period of two to six weeks, a fundamental question arises as to whether the renal lesion has completely healed or subsided temporarily, only to progress into transitional nephritis followed by a progressive degeneration terminating eventually in death from uremia or heart failure.

Often there is failure to diagnosis the acute phase of nephritis because there are mild forms in which the typical picture of hematuria, albuminuria, hypertension, and edema is lacking. It is these cases which are unrecognized, undiagnosed, and untreated that pass insidiously into the chronic form of the disease without the patient being aware of the presence of an illness. When the chronic phase sets in, there is such a variability of symptoms that proper interpretation of the clinical picture is difficult. At times the patient may have all of the five syndromes of nephritis present at the same time: the urinary, hypertension, edema, azotemia, and uremia. At other times one or the other syndrome dominates the picture, so that the patient appears to have some other disease, such as lipoid nephrosis or malignant hypertension. Rarely the patient may develop the salt-losing or potassium-losing nephritis, which may modify the general appearance of the case completely. However, as the natural history of the disease unfolds, it is easy to see that chronic glomerular nephritis is the basic disorder, even though there have been periods when the disease has assumed other characteristics.

The mere enumeration of the sequence of events in the natural history of nephritis would not be sufficient justification for a report such as this. It is our purpose to seek reasons why the events occurred and which factors influenced the onset and progress of the disease. In discussing the natural history of nephritis we have selected 30 patients treated from 10 to 34 years after the acute stage. During this analysis, emphasis has been placed upon factors which may influence prognosis, such as hypertension, infection, and adequate treatment. Why some patients live for a few years and others live many years has been a subject of investigation for a long time.

Presentation of Data

During the past 30 years several hundred cases of glomerular nephritis have been studied at Milwaukee County Hospital, but in most of these patients the period of observation has been under 10 years. In 30 selected cases, however, which have come under the personal observation of one of us (F. D. M.), the patients have been followed over many years through the various chronic

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phases, in some instances from the unmistakable acute stage.

Of the 30 patients, 15 are dead, 14 are living, and the final outcome in 1 is unknown. Acute nephritis was observed in 14 of them (Table 1). From the subsequent

TABLE 1.—*Incidence of Known Acute Glomerular Nephritis in Patients with Chronic Glomerular Nephritis*

	Known Acute Stage	No Acute Stage
Living	9*	6
Mean duration	(16.0 yr.)	(19.2 yr.)
Dead	5	10
Mean duration	(14.2 yr.)	(17.7 yr.)
Total	14	16

* 1 unknown.

clinical course, it is apparent that all these patients progressed to the chronic stage, as shown by the appearance of any one or all of the signs and symptoms of hypertension, anemia, and diminished renal function. This has been further substantiated by studies of the results of blood chemistries, Volhard dilution and concentration tests, Addis counts, determination of 24-hour quantitative protein, urea clearance, P.S.P. excretion, and, in some cases, renal clearances with mannitol and P.A.H. In the 16 patients in whom the acute phase was not observed, appropriate studies were done to rule out such diseases which could cause diminished renal function, such as pyelonephritis, polycystic kidney, essential hypertension, tumors of the kidney, renal amyloidosis, diabetic glomerulosclerosis, and collagen diseases. In some the diagnosis was confirmed by autopsy.

An analysis as to sex and race incidence is presented in Table 2.

The period of observation of the patients with their present status is presented in Table 3.

Of the five chief clinical syndromes, proteinuria was a persistent finding throughout the course of the disease and was the most

TABLE 2.—*Sex and Race Incidence*

Sex	Race		Total
	Caucasian	Negro	
Male	15	2	17
Female	10	3	13
Total	25	5	30

reliable diagnostic sign. On routine urinalysis, however, a negative qualitative protein reaction was often found in some patients during the transitional phase. However, when a 24-hour quantitative protein was checked, there was generally an excretion of 100 to 200 mg., which we consider abnormal. There was no demonstrable correlation between the amount of proteinuria and the outcome or duration of the disease. The

TABLE 3.—*Present Status of Thirty Patients*

Observation, Yr.	Status			Total No. Patients
	Living	Dead	Unknown	
10-15	4	9	1	14
16-20	5	4	0	9
21-34	5	2	0	7
Total	14	15	1	30

occurrence of gross hematuria in the acute stage or in acute exacerbations of the disease did not influence the course of the disease. In the patients who had a marked initial decrease in renal function as a result of the acute episode, it was found that there was no remission or long periods of relative stability of renal function in the transitional phase. Those patients who had a slight initial impairment of renal function had a gradual diminution throughout the course of their disease and, therefore, had a longer life expectancy.

If a diastolic pressure of 100 mm. of Hg was consistently found, hypertension was considered to be present. It occurred after the acute phase of nephritis had passed in 21 of the 30 patients (70%) (Table 4). Hypertension develops in the transitional stage, that is, before the onset of azotemia.

TABLE 4.—*Incidence of Hypertension*

Hypertension	Living	Dead	Total
Present	6	15	21
Absent	9*	0	9
			30

* 1 unknown.

Fifteen of the twenty-one patients who developed hypertension have died. There was no significant difference in the degree of diastolic blood pressure elevation in the transitional stage between the group of patients who died and those who are still living. However, the average duration of life after the development of hypertension in the group who died was 4.03 years, as compared with a 10.5-year mean duration of hypertension in the six living patients. Hypertension is a consistent finding once nitrogen retention develops. It was present in 12 of 13 azotemic patients, the one exception being a patient who had salt-losing nephritis. Of seven patients dying with uremia, the syndrome of malignant hypertension was present in all. Of our 14 patients living with chronic nephritis, 8 have no evidence of hypertension. One patient whose present status is unknown had no hypertension after 11 years' observation (Table 5).

TABLE 5.—*Duration of Hypertension*

	No.	Average Duration, Yr.
Died with hypertension	15	4.03
Living with hypertension	6	10.5
Living without hypertension	9*	17.4

* 1 unknown.

Cardiac complications, as shown in Table 6, are a frequent finding and may be a result of hypertension. However, they are not the chief cause of death, as found in Table 7.

Seven of the thirty patients had the nephrotic syndrome some time during the course of the disease. Eight patients who did not have the nephrotic syndrome at any time showed evidence of edema only late in the course of the nephritis, which was interpreted as being on a cardiac basis.

TABLE 6.—*Cardiac Complications*

Abnormal electrocardiogram	16
Cardiac hypertrophy on x-ray	14
Congestive heart failure	8
Myocardial infarct	2
No complications	9

Of 15 patients who died with chronic nephritis, the cause of death in 7 was found to be uremia. All the causes of death are tabulated in Table 7.

TABLE 7.—*Cause of Death in Fifteen Patients*

Uremia	7
Cardiovascular accident	3
Cardiac	4
Unknown	1

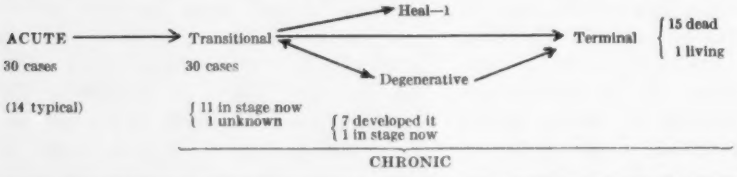
All histories were closely reviewed to determine if any acute infection would cause an exacerbation of nephritis. In six patients such evidence was found. The acute infection caused an increase in the proteinuria and hematuria in the six patients, and in two of them, a return of facial edema. Five of the acute infections involved the upper respiratory tract, and one was a case of rubeola. Unfortunately, during this period of observation, bacteriologic studies such as those by Rammelkamp were not available. In two other patients who were hospitalized during the course of an acute upper respiratory infection, no increase in the activity of the nephritis was observed. In four patients there was an antecedent history of rheumatic fever, but in none of these patients has a rheumatic cardiac lesion been demonstrated.

The female patients were evaluated to determine the course of their disease during pregnancy. Only 5 of the 13 patients became pregnant after their chronic nephritis had become established. Two of these patients had uneventful pregnancies. One of these patients, even though a hypertension of 180/100 was present for many years, had no increase in activity of the disease during

four pregnancies. Three patients had complications during pregnancies. One developed the nephrotic syndrome with one pregnancy and during a second had an increase in proteinuria and hematuria with return of facial edema. Since this occurred in the first trimester of pregnancy, it was not thought to be a toxemia of pregnancy. A second patient developed a full-blown eclampsia which resulted in fetal death. The third patient, although previously having delivered six children, had one pregnancy terminate in fetal death after caesarean section and had two abortions in the second trimester.

Although the course in all of these patients with chronic nephritis is of interest and importance because of the long duration of study, (Table 8) there are a few cases which, in addition, have interesting features which have developed in the long course. The cases reported in another section of this paper illustrate the following characteristics: a healed chronic nephritis, a long transitional and long terminal phase of chronic nephritis, a case of nephrotic edema which has been considered to be lipoid nephrosis, and chronic glomerular nephritis with the salt-losing syndrome.

TABLE 8.—*Course of Thirty Patients with Glomerular Nephritis*



Comment

Acute nephritis may take one of several courses. In a study of 205 patients by Murphy and Peters [1] the courses were as follows: (*a*) Heal completely 34.4%, or 70 of 205 patients)*; (*b*) Die in the acute stage (12.6%, or 26 of 205 patients), and (*c*) Pass into the transitional stage and become chronic (36%, or 74 of 205 patients). In this study the fate of 17% of these patients was unknown (Table 8).

Just which cases will heal completely after the acute phase and which will become chronic is a matter of much conjecture. We agree that the clinical severity of the acute episode is not an indication of a bad prognosis.† Neither does the degree of albuminuria seem to affect it, unless, as has been pointed out by Rudebeck,[4] the initial albuminuria exceeds 10%, in which case it appears to be associated with a greater risk of a fatal outcome in the acute or subacute stage. Hematuria and the degree of edema are not prognostic factors.

In acute nephritics who are markedly hypertensive, the risk of chronic nephritis seems to be higher.[4] Rennie [5] is also of the opinion that the hypertension is the best early indication of a progressive lesion. Out of his 14 patients with hypertension when first seen, 8 died of uremia and only 1 of the remainder improved.

In our experience those patients who did not have an overt acute phase were found to live longer than those patients having a definitive attack of acute nephritis. In all but one of our patients having a known acute nephritis, hypertension definitely was present, whereas in those patients not having known acute nephritis, it can only be conjectured whether hypertension was present. Perhaps it is hypertension that brings an episode of acute nephritis to the level of

* A recent survey of these patients has indicated that healing was complete, and none are included in the present study of 30 cases.

† References 2 and 3.

clinical recognition and, in addition, may be a prognostic factor.

Chronic Nephritis de Novo.—Since nephritis often becomes manifest in the chronic stage without an acute phase being evident in the patient's history, it has been disputed whether the acute and chronic form are one and the same disease or two separate diseases with different etiologies. Generally speaking, physicians, such as Aldrich and Boyle,[6] who treat children believe that the two are different diseases, and, in their series, most of their children made fairly complete recoveries. However, other physicians, such as Addis,[7] who treat adults, believe there is only one nephritis and that the chronic form develops after an acute phase which may have been so mild that it was unrecognized, untreated, and passed insidiously into the chronic form. These are patients with so-called primary chronic glomerular nephritis, or chronic nephritis *de novo*, who have had no previous history of an acute phase.

We do not believe there is such an entity as a primary chronic nephritis. We believe that acute nephritis, either clinically present or hidden, has been present in every case of nephritis. In our series, 16 patients had chronic nephritis without a known acute phase. Every patient who ultimately has chronic nephritis had acute nephritis of some degree in the beginning of his illness. From the unpublished studies of one of us (F. D. M.) and Rammelkamp[8] it is known that patients may have the urinary picture of acute nephritis without any clinical symptoms or other signs of the disease.

Chronic Nephritis.—When has the disease become chronic? There has been much discussion regarding this point.[9] It is generally agreed that nephritis is chronic when the process becomes irreversible, which in the past was considered to occur within six months. However, more recent observations show that a patient with chronic nephritis may heal after two or more years. This healing of a long-standing nephritis is illustrated in Case 1.

Addis[7] used to think there was no chance of healing if the lesion continued two years after the onset. "We are glad to be able to correct this gloomy view," he says, and now he reports five adult patients in whom healing occurred well after the two-year period. As he points out, there is never complete restoration and healing is always with defect. However, it is always wise to reserve judgment on healing, as it is a well-known characteristic of chronic nephritis to go through periods of remission alternating with mild crisis. Whether this is a steadily advancing disease or whether it is a manifestation of renewed little acute attacks, it is difficult to answer. These attacks may be considered as acute exacerbations, but they may really be independent acute attacks caused by the same factor which was responsible for the initial attack.

When nephritis has become chronic, it assumes a clinical course which is characterized by three stages. These periods are fairly distinguishable but not absolutely so. There may be overlapping as the patient goes from one period into the other. Many cases fail to progress through the various stages and pass from the transitional into the terminal stage without having evidence of an intermediate degenerative period. The stages are as follows: 1. Transitional (or so-called "latent period"); 2. Degenerative nephritis, or the period of the nephrotic syndrome; 3. Terminal nephritis.

Stage 1.—After a stormy course of acute nephritis, the patient at times appears to recover so completely that ordinary tests reveal that the kidneys are well on the way to complete recovery. Frequently, however, this recovery is more apparent than real. As a result, the first period of chronic nephritis may pass unnoticed for a long time. It may last for a number of months or even years before events become prominent enough for further investigation. The average duration of the transitional stage in our present series was 15.7 years.

One of the characteristic features of Stage 1 is that the specific gravity of the

urine remains quite unmodified during the first part of the transitional phase. Proteinuria, of course, is present on quantitative analysis, as it is in all stages of chronic nephritis. A decided elevation of the number of red cells, pus cells, and casts on the Addis count is also present. It is the finding of these microscopic evidences in the urine following the acute phase that designates the patient is in the transitional period of chronic nephritis, because other symptoms of chronic nephritis are missing.

Latent nephritis has been considered an objectionable term, according to Leiter,[9] because of the variety of its connotations. We are in agreement with this opinion because the time limits of the latent period have not been precisely defined. The latent period is considered by most to be the first period of chronic nephritis in some instances. In others, however, it indicates the stage of transition which follows the acute attack, when complete restitution to normal is slow to occur. Some patients may become chronic, but many others return to complete healing. We prefer the term "transitional stage," which begins six to eight weeks after the initial attack of acute nephritis. It extends to the appearance of azotemia. The period of transition is one of the most important periods, as the ultimate fate of most patients is sealed at this time.

Hypertension usually makes its appearance in the latter half of the transitional phase and is, we believe, the most practical index that the disease is progressing. It is the syndrome which we have always considered as carrying a bad prognosis.

When hypertension has been established only a few months in a patient with chronic nephritis, we find we are unable to predict accurately whether the patient will fall into the group with a short life expectancy (that one which lived only 4.03 years after hypertension developed) or into the group which has survived 10.5 years. However, with the passage of time, the survival rate of patients having nephritis with hypertension is closely correlated with the degree of impairment of kidney function. In those patients who have had hypertension for three or four years and are still able to concentrate urine to 1.020 on the Volhard test and excrete 35% to 40% of P.S.P. in one hour after the intravenous injection, the prognosis for several more years of life is much better than in those patients who fall below these standards.

Whether control of the hypertension with the agents currently available will significantly alter the prognosis cannot be stated at this time. Long-term investigation will be necessary.

Hypertension once established has no consistency as to level. There may be marked fluctuations in the systolic and diastolic levels in any one patient during the course of his disease. The cause of this is unknown. The height of the diastolic blood pressure in the transitional phase has not been found to be of value as a prognostic sign. There was no significant difference in the diastolic pressure during the transitional stage between the group of patients who died and those who are still living in our series.

When the hypertension persists, cardiac hypertrophy follows. Along with the hypertension, arteriosclerosis and the sequelae of this complication develop, so that in some instances there is a disease developing within a disease. At this period the heart may suffer all the consequences due to these diseases. Seventy per cent of our patients manifested cardiac disease in some form. It has aptly been said that the hidden danger in nephritis is often the cardiac failure. However, the clinician must be careful in his treatment of the patient not to neglect the underlying renal condition while the cardiac symptoms and signs are in prominance. The role which each plays in contributing to the clinical picture of the patient must be recognized.

We realize that at times, despite most careful examination, it is difficult to say whether the lesion is healing or becoming degenerative. Early in the transitional phase the diagnosis of chronic nephritis is difficult

to make, but it becomes relatively easier as the transitional phase progresses. With the modern use of clearance tests, diagnosis is made much easier. The ordinary conventional tests, as the P.S.P. and urea clearance and concentration ability, may not be significantly reduced in the early stage, but precise measurements of renal function, as pointed out by Earle,[10] may show definite functional impairment. A thorough understanding and an early recognition of the transitional period is important if the progress of the nephritis is to be controlled.

In the early months of this stage there must be a continuation of the treatment employed during the acute phase. An adequate period of rest is essential. Holton [11] has challenged an article by Åkerrén and Lindgren,[12] who drew the conclusion that clinical recovery from acute nephritis has no dependency on the period of rest in bed. Holton concludes that these observations do not permit any change in the current principles of treatment with rest in bed for a sufficiently long time. The low-protein diet and the elimination of infection by the use of antibiotics also play an important part in bringing about healing or quiescence of an active period.

Addis [7] believes that the latent or transitional phase comes to a close in one of three ways: (*a*) Heal; (*b*) A small number pass into the degenerative stage, and (*c*) There may be the gradual transition from the latent directly into the third stage without the second stage appearing.

Stage 2.—The second period of chronic nephritis is designated as the degenerative stage. Edema is the dominating clinical syndrome in this stage. The patient develops massive pitting edema of all parts of the body. Degenerative changes have taken place in the nephron, but chiefly in the glomerular membrane, so altering its permeability that large amounts of serum protein, chiefly albumin, pass through it. A fall in the serum albumin to levels of 2.0 gm/100 cc. or less occurs. This is associated with a proteinuria usually greater than 10 gm/24 hours, which is chiefly the result of glomerular leakage. Hypertension may or may not be present in this stage.

During the second stage, the retention of fluid in the tissues and interstitial spaces leads to a lessened outflow of urine. Hyaline and granular casts and a few red blood cells and epithelial cells predominate in the sediment. It must be emphasized that the specific gravity of the urine in this stage is not greatly impaired. It ranges from 1.010 to 1.020. The various functional tests are not badly distorted, although the more delicate ones show a slight reduction of kidney reserve in some cases and a greater degree of renal insufficiency in others. The speed with which the kidney reserve diminishes is hard to gauge. However, the modern tests of precision are helpful. The factors which enter into this diminution are still difficult to comprehend.

Doubly refracting lipoids are seen in the urine as a manifestation of hypercholesterolemia. In the past it was thought that these were diagnostic of the degenerative stage, but now it is known they occur in a wide variety of disorders.

Doubly refracting lipoids in the urine, hypercholesterolemia, generalized anasarca, and hypoproteinemia without azotemia and hematuria were considered characteristic of genuine lipoid nephrosis. Contrary to the opinion of some observers, the identity of genuine lipoid nephrosis has not been settled. It is generally agreed that the glomeruli which formerly were considered normal are the site of degenerative changes in the basement membrane of the glomerular tuft and in the endothelium and epithelium. These changes are revealed by special stains. The exact nature of the change is still not entirely known. However, there is a point which has failed to receive the consideration due it. As was pointed out by Murphy and co-workers,[13] aside from the academic interest involved around the pathologic process going on in the kidney, the patients with this disorder are known to have a better prognosis than the average patient with

chronic glomerular nephritis, and most of them recover completely or almost so. Allen's rather extensive review of the nephrotic syndrome [14] emphasizes that most cases of so-called genuine lipoid nephrosis are really diffuse membraneous or lobular glomerular nephritis. The arguments regarding the histological changes are probably less important than the fact that patients with the clinical features of genuine nephrosis are apt to have a prolonged life and perhaps become entirely well.

Case 3 in this present series was reported in 1938 and now after 26 years shows a minimal diminution of renal function. Is this a case of chronic glomerular nephritis with the nephrotic syndrome which has healed or is this one of genuine lipoid nephrosis with almost complete restitutio ad integrum? However it may be, the patient is now quite asymptomatic.

Not all patients with chronic nephritis pass into the second stage from the transitional stage. In our group of patients, only 7 of the 30 developed the nephrotic syndrome. From an analysis of the case histories, we were unable to find any antecedent factors which would serve to differentiate this group of patients from those patients who did not develop the nephrotic syndrome. The course of patients with the nephrotic syndrome from the bedside and laboratory standpoint was identical with the other patients until the appearance of the anasarca. It may prove that direct visualization of the kidney such as given by needle biopsy will be necessary to predict which patients will develop this stage. We have been unable to determine factors in the clinical course which will allow for an estimation of the severity of the stage or its duration.

The average duration of the nephrotic stage was about 18 weeks. This does not include one patient who had this stage for 3.5 years. From our experience, both in this group of patients and in our other short-term observation group, it is striking that in an occasional patient the edema will recede and the 24-hour urinary protein will greatly diminish without any significant alteration of the serum albumin or cholesterol. At this point it is difficult to tell by physical examination that the patient is still in the second stage.

While it is thought that renal edema is dependent upon the changes in the osmotic hydrostatic equilibrium, this is not the complete answer. The kidney may be the central organ in regulation of plasma protein, but there are many other factors concerned in the synthesis of protein to various parts of the body. However, the further discussion of this intricate problem is beyond the scope of this presentation. Suffice it to say that while edema is a challenging problem it must be admitted that there are many general metabolic factors which may come into play that are still unknown causing the edema.

The appearance of the nephrotic syndrome in the course of chronic nephritis has never been considered to denote a more serious prognosis. However, in this series, of the 15 patients who died, 5 had the nephrotic syndrome, as opposed to 2 in the living group. It may be that the life expectancy seems to be shorter when the patient has the degenerative phase of chronic nephritis. Further observation on this point is being made.

Most frequently as the edema disappears the patient returns to the transitional stage where he may remain for many years. For unknown reasons he may again return to the degenerative stage, although more than two distinct episodes of nephrotic edema are unusual. Occasionally the patient may progress directly to the terminal stage. Speculations have been made regarding the cause of remissions and crises, but so far they are merely speculations, and the exact mechanism involved is not understood. Therefore, we believe that if we stick closely to the facts at hand and remember what the natural history of the disease teaches us, we will be in a better position to evaluate and manage the patient with this disorder.

Control of infection with antibiotics is important in the second stage because the edema and other changes going with the nephrotic syndrome render the body less resistant to infection. The diet has always been considered of great importance. Even Bright[15] recognized this. As he states, "A great deal depends upon the diet. Where milk is grateful if it fits easily on the stomach and is freely digested, I believe it to be one of the best aliments which can be taken. Like animal food frequently agrees. Tea should be avoided. All badly cooked vegetables and fruits will be found injurious. The great rule is to avoid everything which obviously deranges the stomach and to take nutritive but not stimulating food. The less of wine and spiritous liquors taken the better. . . ."

Epstein[16] popularized the high-protein diet in an attempt to elevate the lowered plasma albumin. There is no unanimity of opinion whether to use a high- or low-protein diet. It would seem that an adequate amount, such as 0.5 to 1 gm. per kilogram of body weight per day, is optimal. Because of hypercholesterolemia, fats, particularly cholesterol, are also restricted. Chlorides should be kept low, and adequate vitamin and caloric requirements must be met. A low-salt diet of from 0.5 to 1 gm. of salt daily is administered to control edema. However, in some patients if the sodium becomes too depleted, chlorides may accumulate in the tissues and the low-salt syndrome result. If not corrected, the signs and symptoms of nephrosis already present may be augmented.

Diuretics have been considered dangerous, as it is a general belief that they do more harm than good. We prefer not to use the mercurial diuretics in this stage. The modern treatment of the nephrotic syndrome involves the use of corticotropin (ACTH) and cortisone. The benefit from the treatment with these hormones is unequivocal, as stated by Riley[17] and Luetscher and Deming.[18] But the use of these hormones at best only controls the edema of the nephrotic syndrome. Whether its rigid use may alter the over-all prognosis can only be determined by a much longer period of observation. It should, however, prove useful in the study of the mechanism of diuresis.

Stage 3.—The onset of the third and terminal stage of chronic glomerular nephritis is heralded by the appearance of azotemia. This is the stage of renal failure, the result of severe glomerular and tubular damage. Although treatment may make the patient comfortable and prolong his life, the ultimate outcome is death. There is no possibility of healing at this stage with restitution of normal function, since too many nephrons have been lost to the disease process. The average duration of the terminal phase in the 10 patients in this series who died was found to be 1.1 years. This does not include one patient (Case 2) who lived for 11 years in the terminal phase. Two patients are at present living in the terminal phase, and they have survived 1.75 and 2.33 years.

During this period, polyuria appears, since the specific gravity of the urine falls to the 1.002 to 1.012 range. With the low concentrating power of the kidney, a large amount of urine must be passed in order to excrete the metabolic end-products. Only by the mechanism of polyuria can the blood urea be kept within reasonable limits. Fortunately, these patients usually have a spontaneous thirst, which will ensure an adequate urine volume. However, if the patient becomes dehydrated, large quantities of fluid must be forced to keep up the urine output.

Hypertension is a consistent finding in patients in the terminal phase. It occurred in 12 of 13 patients in this series having azotemia. Cardiac hypertrophy, one of the results of prolonged hypertension, will ultimately lead to congestive failure. This is the usual cause of edema in the terminal phase and not that which is the result of abnormal permeability of the glomerular membrane to protein.

The hypertension is usually much higher in the third stage than in any other stage and assumes at times the proportions of malignant hypertension. This occurred in 7 of the 21 patients who had hypertension. It is important at this time to differentiate those patients with malignant essential hypertension from those patients with malignant hypertension arising from chronic nephritis. As pointed out by Page and Corcoran,[19] differentiation is significant, for malignant hypertension progresses rapidly from the stage of impending uremia to death, whereas chronic nephritis may, with proper care, remit or stabilize at this level for long periods. Page and Corcoran further emphasize that the renal functional pattern in chronic nephritis is one of predominant reduction of glomerular filtration, and as the terminal phase advances, tubular secretory capacity reduces rapidly to levels well below those seen in malignant hypertension.

When renal insufficiency becomes pronounced, serious electrolyte disturbances occur in the extracellular fluid compartment. There is retention of nitrogenous products and acid metabolites due to an actual decrease in the amount of glomerular filtering area. The accompanying loss of tubular function results in lack of ability to conserve fixed base and to excrete such ions as potassium. Hypochloremia, hypocalcemia, and hyperkalemia and acidosis make their appearance and induce new clinical patterns.

Normochromic anemia which may have appeared late in the transitional phase becomes more pronounced in the terminal phase. The pathogenesis of this anemia is not definitely known, and it responds poorly to treatment.

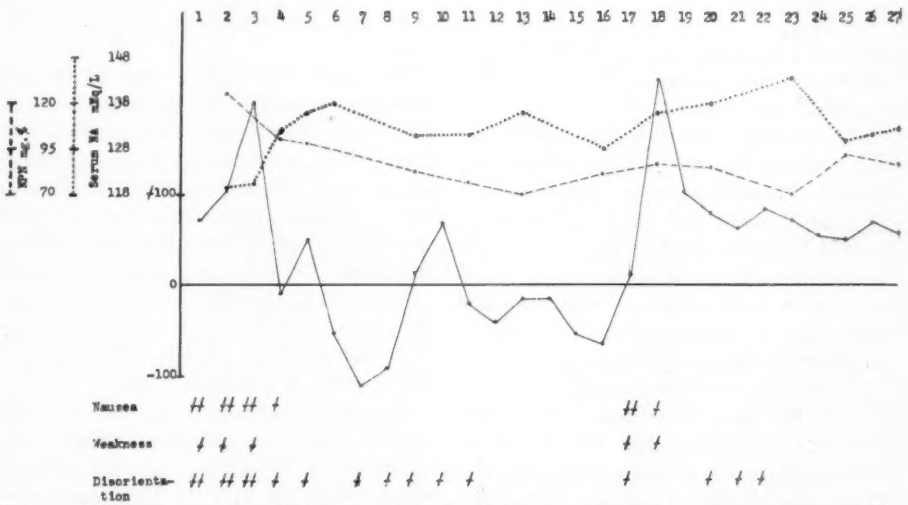
In 7 of 13 patients with azotemia in this present series there was progression to genuine uremia and death. Uremia is the most frequent cause of death in the terminal stage, and if it were not for the deterioration of the cardiovascular system, would probably be the sole cause of death in these patients. Its mechanism is unknown, but it certainly is not the accumulation of nitrogenous products alone.

The clinical picture of the uremic syndrome is variable depending on the degree of involvement of the organ systems. Anorexia, nausea, vomiting, and diarrhea may be prominent. Hemorrhagic phenomena, such as ecchymoses, epistaxis, hematemesis, and melena, may predominate. Pericarditis is often a finding. However, when the central nervous system is involved the patient's death is near. He progresses through stages of mental depression and confusion and then to irrationality, muttering delirium, and oftentimes convulsions. Finally, coma develops, from which the patient usually fails to recover.

All symptoms in the terminal stage of the disease must not be ascribed to uremia, even though the blood urea is elevated. As in Case 4 and the Figure, electrolyte disturbances, such as a low-serum sodium, must be ruled out. Proper treatment, in this case increased amounts of sodium chloride, results in the correction of a disturbed sensorium. Convulsions occasionally occur in association with a low serum calcium and sometimes can be mitigated or controlled by the administration of parenteral calcium solutions.

It is important to emphasize that although renal function tests are very low and that renal insufficiency is imminent, it is surprising how long the patient can survive. Case 2 had azotemia for 11 years, during most of which time he was able to lead an active business life. One episode of severe azotemia was survived with vigorous therapy.

Patients in this stage adjust surprisingly well to moderately high degrees of azotemia, marked disturbances of acid-base balance, and moderately severe anemia. Intelligent management is most important in the prognosis of the terminal stage. The patient must not be abandoned, for he can continue to be a comfortable, productive member of society for months and even years with careful management.



Balance studies in a case of salt-losing nephritis. Correlation of sodium balance and clinical symptoms. Periods of salt loss are accompanied by or immediately followed by nausea, vomiting, weakness, and disorientation.

We are in accord with Keith and Odel,[20] who believe that the outlook for the patient with chronic glomerulonephritis is not as gloomy as was thought and that certain complications, as fluid and electrolyte imbalance, formerly uncontrollable, now respond to proper treatment.

Our study of these cases over a period of years teaches us that as the disease progresses, certain factors modify the progress of this chronic disorder. The control of fluids and electrolyte balances is a recent achievement which has done a great deal to prolong the life of some. The proper use of a low-protein diet and a high fluid intake may help immeasurably. The advent of the antibiotics has been important in the control of intercurrent infections which have been so damaging in years gone by. Furthermore, the newer antihypertensive drugs have played a beneficial role in controlling the hypertension which is considered to be such an unfavorable complication. As we have watched these patients pass from one stage into another, from crises into remissions with the various syndromes coming and going, it is truly remarkable how long life can be prolonged by adherence to simple and positive methods of management.

Summary

In discussing the natural history of glomerular nephritis, 30 patients studied at Milwaukee County Hospital from 10 to 34 years after the acute stage were selected and are reviewed, with emphasis placed upon factors which may influence prognosis. Of the 30 patients, 15 are dead, 14 are living, and the final outcome in one is unknown.

We believe acute nephritis, either clinically present or hidden, has been present in every case of nephritis. In our series, 16 patients had chronic nephritis without a known acute phase. Acute nephritis may take one of several courses: (*a*) Heal completely; (*b*) Die in the acute stage, or (*c*) Pass into the transitional stage and become chronic. Just which cases will heal after the acute phase and which will become chronic is a matter of much conjecture. This is discussed.

When nephritis has become chronic, it assumes a clinical course which is characterized by three stages: (*a*) The transitional stage; (*b*) The degenerative phase, and (*c*) Terminal nephritis.

Acute upper respiratory infections may cause an acute exacerbation of the disease, but the ultimate course in this series was apparently not affected.

The duration of the transitional phase was 15.7 years in this series, during which the patients frequently were asymptomatic. Proteinuria, which was consistently present, could not be correlated with prognosis. If the initial renal impairment in this stage was found to be slight, a more gradual diminution in function occurred which gave the patient a longer life expectancy.

Diastolic hypertension occurs in the latter half of the transitional phase. It is the most practical index that the disease is progressing, and it carries a bad prognosis. Twenty-one of thirty patients (70%) developed hypertension. No consistent factors were found which enabled the onset of hypertension to be predicted. The average duration of life after the development of hypertension in the group who died was 4.03 years, as compared with 10.5-year mean duration in the living patients.

The survival rate of patients having nephritis with hypertension is closely correlated with the degree of impairment of kidney function. In those patients who had hypertension for three or four years and are still able to concentrate urine to 1.020 on the Volhard test and excrete 35% to 40% of P. S. P. in one hour or after the intravenous injection, the prognosis for several more years of life is much better than in those patients who fall below these standards.

Not all patients with chronic nephritis pass into the second stage—that of the nephrotic syndrome. Seven of the thirty patients in this series did so. Until the onset of the anasarca, their course was identical with the other patients. The average duration of the second stage was 18 weeks. The possibility exists that the nephrotic syndrome may shorten the course of chronic nephritis. Of the 15 patients in this series who died, 5 had the nephrotic syndrome, as opposed to 2 in the living group.

The onset of the third stage of chronic nephritis is initiated by the appearance of azotemia. There is no recovery from this stage, which, in this series, lasted an average of 1.1 years. Duration of life, though ultimately dependent on the degree of renal impairment, can be markedly influenced by treatment. Hypertension was consistently present, being observed in 12 of 13 patients who were azotemic. Of seven patients dying with uremia, the syndrome of malignant hypertension was present in all.

Cardiac complications were a frequent finding (70%) but were not the chief cause of death in this series. Uremia was the terminal episode in 7 of 15 patients who died.

In a few cases in this series, interesting features developed during the long course of the chronic nephritis. Illustrative cases are presented, showing the following characteristics: A healed chronic nephritis, a long transitional and long terminal phase of chronic nephritis, a case of nephrotic edema which was considered to be lipoid nephrosis, and chronic glomerular nephritis with the salt-losing syndrome.

Miss Opal A. Kelly, B.S., M.T., gave technical assistance in performing the renal function studies, and Miss Grace M. Treutinger, Ph.B., gave assistance in the preparation of the manuscript.

Report of Cases

Case 1 (Healed Chronic Glomerular Nephritis).—A 28-year-old white man entered Milwaukee County General Hospital for the first time at the age of 16 years. For eight weeks prior to admission the patient had had a thrombophlebitis of the left leg, which had not responded to treatment. There was no history of a recent upper respiratory infection or of antecedent renal disease. The diagnosis of acute glomerular nephritis was made on the basis of bilateral peripheral edema and the urinary findings of proteinuria and hematuria. Hypertension, hemorrhagic retinitis, and azotemia were not observed.

The patient was hospitalized for seven months, during which time the thrombophlebitis subsided. Proteinuria changed very little and averaged about 7.5 gm/24 hours. The hematuria diminished but was never lower than 5,500,000 RBC's on a 12-

TABLE 9.—*Healed Chronic Glomerular Nephritis**

Date	Oct., 1944	Feb., 1945	Feb., 1946	Sept., 1946	March, 1947	Jan., 1949	Nov., 1950	March, 1955	April, 1956
Proteinuria, gm./24 hr.	7.0	8.9	5.9	1.3	0.6	0.1	0.06	Neg.	Neg.
Urine RBC, Addis	30,400,000	6,770,000	2,600,000	990,000	680,000	280,000	650,000	1,000,000	183,000
NPN., mg./100 cc.	31.7	35	34	38	34	34	32	33	
Hgb., gm/100 cc.	15.5	15.0	15.0	16.0	15.0	15.5	15.0	15.0	
B.P., mm. Hg.	115/85	130/75	134/75	125/75	120/80	128/70	130/76	122/74	120/72
Fundi, K-W grade	1	1	1	1	1	1	1	1	1
Edema	1+	Tr.	0	0	0	0	0	0	0
Comment	Acute nephritis; Aug. 1944	Kidney biopsy, glomerulo-nephritis, low grade	Acute tonsillitis	Asympto-matic	Asympto-matic; in Army May-Nov., 1947; disch. proteinuria	Asympto-matic	Asympto-matic; R.B.F., 1,306; R.P.F., 692; G.F., 97; $T_{m_{PAH}}$, 124	Asympto-matic; R.B.F., 1,459; R.P.F., 671; G.F., 101; $T_{m_{PAH}}$, 100	Asympto-matic; Addis count done 2 wk. after U.R.I.

* Case 1, 28-year-old white man.

TABLE 10.—*Long Transitional and Long Terminal Phase of Chronic Glomerular Nephritis* *

Date	1934	1940	1944	1952	1954	1955	1956
Proteinuria	1+	1+	5.2 gm./24 hr.	2+	2+	2+	2+
N.P.N., mg./100 cc.	40	36	62	70	103	204-70	170
Edema	0	0	±	±	±	0	0
B. P.	120/80	110/80	160/90	170/100	184/104	140/80	120/60
Comment	Proteinuria present for last 12 yr.		Exertional dyspnea; weakness; ECG, non-specific ST-T, L. B.B.B.	Coronary insufficiency; ECG, L.V.H.	Pyelonephritis treated with tetracycline (Achromycin); low-protein diet		Died with coronary thrombosis

* Case 2, 61-year-old white man.

hour Addis count. A renal biopsy in February, 1945, confirmed the clinical impression of glomerular nephritis.

After discharge in April, 1945, until March, 1947, the patient was hospitalized every three to four months for study. During this period the patient had three upper respiratory infections, and only during one was there a slight increase in the degree of proteinuria and hematuria. By March, 1947, the urinary excretion of protein had decreased to 600 mg/24 hours, and the RBC's in an Addis count were 680,000. The patient was asymptomatic and normotensive. A repeat renal biopsy in September, 1946, had showed residual changes of glomerular nephritis.

In May, 1947, the patient enlisted in the Air Force but was discharged in November, 1947, because of chronic renal disease.

Since this time the patient has been periodically studied in the hospital and as an outpatient. He has no complaints, works daily, and is on a general diet. Renal studies are summarized in Table 9.

CASE 2. (Long Transitional and Long Terminal Phase of Chronic Glomerular Nephritis).—A white man was first seen in 1934, at the age of 39. History revealed that the patient had scarlet fever at the age of 5 years and mastoiditis at 12 years. No history of acute nephritis was elicited. Life insurance was refused when the patient was 27 years old, because of proteinuria. Physical examination in 1934 showed no significant abnormal findings. Laboratory studies were within normal limits except for a 1+ proteinuria.

Until 1940 the patient was asymptomatic, and there had been no change in the clinical or laboratory status. At this time, however, a slight rise in the blood pressure was noted, and ankle edema was present intermittently. The patient began to notice mild exertional dyspnea and easy fatigability. Proteinuria increased, and a moderate normochromic anemia was present, but azotemia did not appear until 1944. Dietary protein restriction (40 gm.) was then instituted. However, in spite of gradual physical deterioration, the patient was able to continue his business.

By 1952, the patient had symptoms of coronary insufficiency, and the electrocardiogram now showed definite evidence of left ventricular hypertrophy, which correlated well with the cardiac enlargement on physical examination. The blood pressure was 180/110. The N. P. N. was 75 mg. per 100 cc., and a persistent 2+ proteinuria was noted. Congestive failure was not a problem.

Because of symptoms of pyelonephritis, in 1954, treatment with wide-spectrum antibiotics was instituted in addition to the continuation of a large daily fluid intake, protein restriction, and symptomatic measures.

While on vacation, in 1955, the patient developed signs of marked renal failure, with a rise of the N. P. N. to 204 mg. per 100 cc. With vigorous therapy during hospitalization it fell to 70 mg. per 100 cc., and the patient was again able to resume his duties.

In January, 1956, the patient experienced severe chest pain, for which he was hospitalized. After

TABLE 11.—*Nephrotic Edema**

Date	July, 1930	Oct., 1930	Jan., 1956
B.P.	110/60	105/60	110/70
Edema	4+	0	0
N.P.N.	31.5	32.0	31.5
A/G	1.6/2.1	4.8/2.5	5.5/2.9
Cholesterol	584	211	315
Urine sediment	RBC, 1-2; WBC, Occ.; casts, 0-1	RBC, Occ.; WBC, Occ.; casts, rare	RBC, 897,000; WBC, 2,272,000; casts, 21,000
24-hr. urine protein	14.3 gm.	Neg.	Neg.
Volhard	1.002-1.012	1.004-1.024	1.003-1.019
P.S.P.	30 & 25	40 & 30	32.5 & 32.5
Comment			R.B.F., 1,059; R.P.F., 540; G.F., 120; F.F., 0.22; Pm., 102

* Case 3, 44-year-old white man.

TABLE 12.—*Chronic Glomerular Nephritis with the Salt-Losing Syndrome* *

Date	1935	Sept., 1946	1953	1954	1955	Feb., 1956	April, 1956
Proteinuria	3+	4+	1+	1+	1+	1.9 gm.	1.8 gm.
N.P.N.	56	B.U.N., 50	B.U.N., 72	123	88	124	85
Edema	1+		0	0	0	0	0
B.P.	136/80	200/105	130/90	132/84	130/90	136/78	140/80
Comment	Acute nephritis after scarlet fever	Uric acid, 10; toxemia of pregnancy; C. section; improvement	P.S.P., 5% 2 hr.; liver function O.K.; anemia			Na, 119; Cl, 75; CO_2, 22; K, 2.8; Ca, 9.8; P, 3.6; salt loser	Na, 139; Cl, 103; CO_2, 21; K, 4.7; Ca, 7.1; P, 3.8; R.B.F., 22.2 cc./min.; R.P.F., 17.0 cc./min.; G.F., 3.2 cc./min.; Tm_{PAH}, 7.2 mg./min.; Addis: RBC, 26,600,000; WBC, 686,000,000; casts, none seen

* Case 4, 40-year-old white woman.

a three-week course he died of a coronary thrombosis. At autopsy the findings of chronic glomerular nephritis were demonstrated in addition to those of pyelonephritis. Renal studies are summarized in Table 10.

CASE 3 (Case of Nephrotic Edema Considered to be Lipoid Nephrosis).—A white man was first seen at Milwaukee County General Hospital on July 25, 1930, at the age of 18 years. For 12 weeks prior to admission the patient had had swelling of the entire body which had begun in the face. Urinary symptoms were absent, except for a decrease in the amount of urine. The patient's past history revealed no similar previous episodes and no diseases of importance.

On admission the blood pressure was 110/60. Funduscopic examination was within normal limits. Anasarca was the outstanding physical finding; it was associated with a left pleural effusion and ascites. The heart was within normal limits.

The patient was hospitalized three months, during which time the edema receded as the serum albumin returned to normal and the proteinuria disappeared.

The patient has been seen intermittently during the past 25 years, at which times the blood pressure and routine urinalyses have been within normal limits. He was rejected for military service in 1942 because of flat feet.

General health has been good except for recurrent attacks of bronchitis and the recent development of a peptic ulcer. There has not been edema or urinary symptoms at any time except the initial episode. Renal studies are summarized in Table 11.

CASE 4 (Chronic Glomerular Nephritis with the Salt-Losing Syndrome).—This white woman, who is now 40 years old, was first seen in 1935, with acute glomerular nephritis which followed in the course of scarlet fever. After a brief period the patient became asymptomatic, but through the years she continued to have proteinuria. There were no exacerbations of her nephritis.

The patient was next seen in 1946, when she was two months pregnant, at which time she offered no complaints. Within five months the blood pressure rose from 120/70 to 200/105. The serum uric acid had increased to 10 mg. per 100 cc. The patient had a true eclampsia, which was complicated by a toxic psychosis. A few days after Cæsarean section, the patient's condition was much improved and there was return of the blood pressure and chemistries to the prepartum status.

In 1953 the patient was evaluated for an anemia, which was determined to be the result of her chronic renal disease.

Throughout 1954 the patient was seen frequently for the complaint of chronic tiredness. The blood pressure was always found to be normal, but the nonprotein nitrogen averaged about 120 mg. per 100 cc. The urine specific gravity was fixed at about 1.010, and a 1+ proteinuria was present. The patient was maintained on a low-protein diet in addition to symptomatic treatment.

During the latter part of 1955 the complaint of "leg cramps" appeared for the first time. There was little change in the clinical or laboratory picture, except that the azotemia was less.

In January, 1956, the patient entered a private hospital for one of her periodic check-ups and while there became depressed, expressed suicidal tendencies, and had frequent hallucinations. She was transferred to Milwaukee County General Hospital. Significant findings are summarized in Table 12 and the Figure. With correction of electrolyte disturbances there was improvement in the sensorium and the clinical appearance. Because of the loss of sodium-conserving ability by the kidney, the patient has been maintained on a high-salt, low-protein diet. Although the patient is in precarious electrolyte balance at the present time, she is able to do her own housework and is relatively asymptomatic.

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The Mechanism and Significance of Protein Excretion by the Normal Kidney

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The supposition that the glomerular filtrate is protein-free is based on the classical experimental studies of Wearn and Richards.[1] They found glomerular fluid, obtained by micropuncture from Bowman's capsule, to be "protein free" or at least to contain less than 30 mg. per 100 ml. of protein, which was the least amount that could be detected by the methods at their disposal. As Addis[2] has pointed out, this supposition might be readily accepted were it not that the volume of glomerular filtrate in man is approximately 180,000 ml. per 24 hours, so that even if the protein concentration was as little as 10 mg. per 100 ml., 18,000 mg. would pass through the membrane daily. Considerations of this sort stimulated workers in the field, so that during the past 10 years our knowledge of the passage of proteins through the kidney has advanced to the point where a fairly comprehensive description of the mechanism of proteinuria is possible.

It is clear through the work of many investigators, notably, Gerard and Cordier,[3] Smetana,[4] Oliver,[5] and Rather,[6] that injected foreign proteins may pass the glomerular membrane and appear in the cells of the renal tubule. Bayliss, Tookey-Kerridge, and Russell[7] have shown that proteins of molecular weight less than 60,000 and including hemoglobin pass the glomerular membrane readily, while proteins of molecular weight 60,000 and over are more completely retained in the blood stream.

Thus, while the glomerular membrane is readily permeable to certain proteins foreign to the host, an insight into the mechanism of proteinuria requires a knowledge of the course of native plasma proteins through the kidney. Evans blue dye (T 1824) forms a firm, stable complex with the plasma proteins. When injected into the blood stream in suitable amounts, it attaches selectively to plasma albumin. Dock[8] took advantage of these properties of Evans blue dye to provide a visible tag for the plasma albumin. He was able to show that following the injection of Evans blue dye into rats, blue droplets appear in the cells lining the proximal convoluted renal tubules. He construed this as evidence for the filtration and subsequent tubular reabsorption of plasma albumin. This work was confirmed by Gilson[9] and later by Sellers and co-workers.[10]

In the latter study, rats were killed at intervals following the intravenous injection of Evans blue dye. Unstained frozen sections were made of the kidney. Blue dye appeared in the cells of the proximal convoluted tubule as early as 90 minutes following its injection. In all instances, the blue dye was first observed occupying the luminal one-third of the tubule cells. As time progressed, more and more of the cell came to be occupied by dye, and as late as seven hours following injection, the blue particles were distributed throughout the cell, from luminal to capillary border. Thus, it appears that a portion of the plasma al-

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bumin passes the glomerular membrane and is reabsorbed at the luminal surface of the proximal tubule cells.

The normal rat excretes relatively more urinary protein than man. Thus, the adult male rat excretes approximately 0.5 mg. of protein per hour.[11] In collaboration with Dr. Sidney Roberts, we conducted an electrophoretic study of the normal urinary protein in the rat.[12] It was found that the protein in normal rat urine consists principally of two fractions having the electrophoretic and solubility characteristics of plasma α-and β-globulin, respectively. Little or no albumin could be detected in the voided urine. This observation has been confirmed by Lewis and co-workers [13] and by Rumsfeld and Baumann.[14]

The proteins present in normal rat urine have been shown to come from the kidney and do not represent contamination from the lower urinary tract.[11] Furthermore, Beiter [15] has shown that proteinuria cannot be produced in animals that have no glomeruli. It appears most probable, therefore, that normal urinary proteins are derived from the plasma proteins by passage across the glomerular membrane. If, as indicated here, the glomerular membrane allows the passage of large plasma globulin molecules, it would seem likely that the smaller plasma albumin molecules would pass into the glomerular filtrate even more readily. The absence of albumin from normal rat urine is interpreted to mean that this protein is more completely reabsorbed by the cells lining the proximal convoluted renal tubule. A similar situation exists in man. Normal human urinary proteins were studied by Rigas and Heller [16] and by McGarry and co-workers.[17] The albumin/globulin ratio of the urinary proteins was found to be the reverse of that of the plasma proteins.

Data of this sort, together with the evidence obtained from the Evans blue dye studies of Dock, Gilson, and ourselves, provide a strong case for the filtration and tubular reabsorption of plasma protein as part of the day-to-day physiological activity of the rat and quite possibly of man.

In order to assess the importance of glomerular filtration and tubular reabsorption of plasma proteins in the over-all economy of the experimental animal, it became necessary to study the order of magnitude of the processes involved. An early attempt to quantitate the protein concentration of glomerular filtrate was that of Dock.[8] Using Bickford and Winton's technique of paralyzing tubular functions by perfusion of the rabbit kidney with ice-cold serum,[18] he obtained protein concentrations of 15-22 mg. per 100 cc. of "glomerular filtrate."

We had demonstrated that when 25 mg. of Evans blue dye is injected intravenously into 200 gm. rats, no measurable amount of free Evans blue dye exists in the circulating blood, and when proteinuria is produced, all of the Evans blue dye found in the urine is protein-bound.[19] It was reasoned, therefore, that Evans blue dye present in the lumen of the nephron is protein-bound and that the Evans blue dye-protein complex is reabsorbed by the tubule cells. Since Evans blue dye is carried into the tubule cell attached to protein, and since it is seen to accumulate in these cells in the form of intensely blue droplets for a period of 24 hours after injection, by measuring the total Evans blue dye content of the tubule cells and the mean ratio Evans blue dye/protein per unit time in the plasma, one can calculate the milligrams of protein reabsorbed by the tubules in combination with Evans blue dye during any desired time interval. When this was done, it was found that plasma protein reabsorption by the cells of the proximal convoluted tubule of the rat kidney proceeds at a rate of approximately 5 mg. per hour. From known glomerular filtration rates and rates of protein excretion in the voided urine of the rat, we can compute that the protein content of the glomerular fluid in Bowman's capsule is approximately 7.5 mg. per 100 ml. From the nature of the experiments performed, we find that 7.5 mg. per 100 ml. is a minimal

figure and that the actual protein content of the glomerular fluid may be in excess of this value. This concentration is well below the limits discernible by the methods employed by Wearn and Richards [1] or by Walker and his co-workers [20] in their micropuncture experiments and is somewhat lower than Dock's figure for the perfused rabbit kidney.[8]

To this point then, the evidence indicates that glomerular filtration and tubular reabsorption of plasma protein is part of the normal activity of the mammalian kidney. In view of the large volume of glomerular filtrate formed each day, protein concentrations in the range described above assume considerable magnitude, and since the quantity of protein in the voided urine is small, we are compelled to consider the metabolic processes in the proximal tubule cells that deal with the reabsorbed protein.

In describing this phase of the mechanism of proteinuria, we are indebted principally to Oliver and his co-workers, who have so carefully studied the fate of reabsorbed protein droplets.

Since plasma protein is continuously being filtered at the glomerulus and reabsorbed by the renal tubules, some mechanism must exist for the disposal of the reabsorbed protein or its breakdown products into the renal vein blood. In Oliver's view,[21] there are two phases of protein reabsorption. There is the diffuse phase, in which the reabsorbed protein is diffusely dispersed in the cytoplasm of the renal cell, and the droplet phase, in which the reabsorbed protein together with mitochondrial substances collect into droplets. In the diffuse phase, the protein may be seen to enter the cell and is at first confined to the area beneath the marginal brush border; as time passes, the protein comes to occupy the entire cell body. No alterations in the cytological appearance of the cells can be seen by the usual methods of observation. This, Oliver explains, is the picture of the tubular disposal of protein in the normal rat and in certain pathological proteinurias in man. If the tubules of the rat are presented with an increased load of native plasma protein, or if a foreign protein such as egg albumen is injected, a different histological picture will be seen. The reabsorbed protein and the mitochondria of the tubule cells coalesce into droplets. These droplets have been shown by Oliver and his co-workers * to contain the reabsorbed protein, as well as a variety of mitochondrial substances, including its rich store of proteolytic enzymes. The droplet may be considered a locus of intense proteolytic activity, and presumably the reabsorbed protein is broken down to simpler compounds before these substances enter the peritubular venous capillaries. Recent work by Spector [24] has clarified the mechanism of protein disposal in the diffuse phase of proteinuria. Employing native rat albumin and γ-globulin labeled with I^{131}, Spector was able to show that the labeled protein enters the tubule cell and becomes incorporated into the mitochondrial fraction. By analogy to Oliver's droplets of proteolytic activity in the droplet phase of proteinuria, it appears that in the diffuse phase of proteinuria the reabsorbed protein may be similarly catabolized by being incorporated into the mitochondrial substance.

Our knowledge of the mechanism of proteinuria may now be extended to include plasma protein catabolism by the cells of the renal tubule, in addition to the processes of glomerular filtration and tubular reabsorption already described. The possible importance of the normal mechanism of proteinuria can be appreciated if we pause for a moment to consider the quantity of plasma protein that may be involved in this never-ceasing process of catabolism in the renal tubules.

As mentioned above, it has been computed that a minimum of approximately 5 mg. of plasma proteins are reabsorbed by the rat tubules per hour. If this protein is degraded by the tubule cells to simpler polypeptides and amino acids, one should be able to demonstrate an increased quantity

* References 22 and 23.

Differences of Plasma Concentration of Free and Total α-Amino-Acid Nitrogen and Polypeptide Nitrogen Between the Renal Vein, the Inferior Vena Cava, and the Abdominal Aorta, Respectively *

Rabbit No.	Difference, Mg./100 Mg.								
	Free Amino Acid Nitrogen			Total Amino Acid Nitrogen			Polypeptide Nitrogen		
	Rv-ART	IVC-ART	RV-IVC	RV-ART	IVC-ART	RV-IVC	RV-ART	IVC-ART	RV-IVC
1	+0.045	−0.27	+0.72	+1.29	+0.13	+1.16	+0.84	+0.40	+0.44
2	+0.31	+0.53	−0.22	+1.25	+1.11	+0.14	+0.88	+0.52	+0.36
3	+0.50	−1.20	+1.70	+1.83	−0.70	+2.53	+1.33	+0.50	+0.83
4	+0.80	−0.43	+1.23	+1.53	−0.08	+1.61	+0.73	+0.35	+0.38
5	+0.44	−0.17	+0.61	+1.84	+0.60	+1.24	+1.40	+0.77	+0.63
6	+0.51	−0.27	+0.78	+1.34	+0.03	+1.31	+0.83	+0.34	+0.49
Mean	+0.50	−0.30	+0.80	+1.51	+0.18	+1.33	+1.00	+0.48	+0.52
S. D.	0.16	0.31	0.64	0.27	0.43	0.77	0.29	0.16	0.18
P	<0.001	>0.05	0.05-0.01	<0.001	>0.05	0.01-0.001	<0.001	0.001	<0.001

* RV indicates renal vein; IVC, inferior vena cava; ART, abdominal aorta.

of these substances in the renal vein blood as compared to blood issuing from structures that are nonspecific insofar as protein catabolism is concerned.

Eliasch,[25] working with the rabbit, has collected nearly simultaneous blood samples from renal artery, renal vein, and inferior vena cava below the entry of the renal veins. These samples were analyzed for their content of free amino acid and polypeptide nitrogen. The concentration of these substances was uniformly greater in renal vein blood than in samples from renal artery or inferior vena cava. A summary of the data is shown in the Table.

An increase in the amino acid and polypeptide concentration in renal vein over renal arterial blood in the presence of nearly identical hematocrit values must mean that these substances are added to the blood stream during its passage through the kidney. While it is possible that amino acids and polypeptides are synthesized in the kidney from simpler precursors, we know of no evidence to support such a view. The increase in amino acids and polypeptides in renal vein over renal arterial blood could occur if larger protein or peptide molecules are undergoing degradation in the kidney. This degradation could represent catabolism of the structural protein of the kidney itself, or, as appears more likely, it is largely the protein reabsorbed from the glomerular filtrate that is being broken down.

The renal arteriovenous amino acid and polypeptide differences tabulated in the Table, though highly significant statistically, are small in magnitude. The extent of the difference is magnified, however, when one considers the large volume of renal plasma flow. It has been calculated that the renal arteriovenous amino acid and polypeptide nitrogen difference of 1.51 mg. per 100 ml. represents the breakdown of approximately 13.5 mg. of protein for every 100 ml. of renal plasma flow. A picture of the mechanism of protein passage through the normal mammalian kidney may now be summarized as follows.

Plasma proteins pass the glomerular membrane and are contained in glomerular filtrate to the extent of 7.5 mg. per 100 ml. or higher. As the fluid from Bowman's capsule passes the cells of the proximal convoluted tubule, these proteins are reabsorbed, plasma albumin being more completely reabsorbed than the plasma globulins. As the proteins enter the tubule cells, they come into intimate contact with the mitochondria. The proteolytic enzymes contained in mitochondria catabolize the plasma proteins into amino acid and polypeptide fragments. These simpler compounds then enter the peritubular venous capillaries and leave the kidney via the renal vein.

The process of glomerular filtration and tubular reabsorption of plasma protein must serve some function other than the mere conservation of these substances, since several lines of evidence outlined above indicate that the reabsorbed proteins are degraded in the tubule cells. A consideration of the quantitative aspects of protein reabsorption may provide a clue to these functions. The protein content of glomerular filtrate in the rat is in the neighborhood of 7.5 mg. per 100 ml. It is highly probable that the majority of protein filtered and reabsorbed by the tubules is plasma albumin. For the sake of simplicity, let us consider that all of the protein reabsorbed is albumin. The circulating blood volume of the 200 gm. rat is approximately 15 cc. At hematocrit values of 50% and plasma albumin concentrations of 4 gm. per 100 ml., this yields about 300 mg. of circulating plasma albumin. Figures from man indicate that 60% of the total exchangeable albumin pool is extravascular.[26] Thus, applying these figures to the rat, the total exchangeable albumin pool is approximately 750 mg.; but the rat reabsorbs 5.0 mg. of albumin per hour, or 120 mg. per day. Hence, 16% of the total exchangeable albumin pool of the rat is reabsorbed and presumably broken down by the renal tubules daily. If these figures approach what may be true values in this species, the kidney may play a major role in

regulating the rate of plasma protein turnover. Thus, one could predict that the rate of plasma protein turnover would fall as the mass of functioning renal tissue decreased. Armstrong, Bronsky, and Hershman [27] have recently reported human data that may be considered to support this hypothesis. They have shown that the turnover time of S^{35}-labeled plasma albumin is markedly prolonged when injected into patients with renal failure as compared with the turnover time of the same protein samples injected into normal control subjects. Alpha- and beta-globulins behaved in a similar fashion, while the turnover times of fibrinogen and gamma-globulins were not significantly different in uremic and normal recipients.

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Treatment in Internal Medicine

NONTROPICAL SPRUE
Pathologic Physiology, Diagnosis, and Therapy

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NONTROPICAL sprue (idiopathic steatorrhea) may be defined as a disease of unknown etiology without specific anatomicopathologic changes [1] occurring in adults living in temperate climates in which absorption from and motility of the small bowel are impaired. Nontropical sprue includes celiac disease (with which it is apparently identical) when it persists into adult life. It does not include sprue syndromes arising secondary to diseases characterized by specific pathologic abnormalities.

Impairment of absorption in nontropical sprue, contrary to early beliefs, affects all nutrients, including fat, protein, carbohydrates, vitamins, minerals, and even water. Although steatorrhea is an easily recognized and characteristic feature of this disease, the fecal content of nutrients other than fat is also increased. For this reason the terms "idiopathic steatorrhea" and "steatorrhea syndrome" are not satisfactory designations for nontropical sprue. Impaired absorption leads to diarrhea with loss of weight, hypoproteinemia with edema and ascites, osteomalacia with hypocalcemia and tetany, hypolipemia, hyponatremia, and hypokaliemia, as well as to some other evidences of deficiency states, including those of all the water-soluble and fat-soluble vitamins. These metabolic disturbances secondary to malabsorption produce some of the essential features of the disease. Their recognition is important in diagnosis. Some of them serve to distinguish the steatorrhea of nontropical sprue from that of pancreatic insufficiency. They are important therapeutically because each merits attention in planning a program of therapy. Whether all the metabolic disturbances demonstrable in nontropical sprue are due to deficiencies caused by impaired absorption or whether some of them are manifestations of primary metabolic disturbances of this disease is a question which has not as yet been completely answered.

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Pathologic Physiology

Impaired Absorption from Small Intestine.—Malabsorption from the small bowel alters the composition of feces and urine, blood, and tissues. The magnitude of the alterations varies with the severity and duration of the disease, its state of activity, and the effectiveness of therapy.

Water: Disturbed metabolism of water in nontropical sprue is evidenced by peripheral edema in the presence of systemic dehydration and by retention of fluid in distended loops of intestine, demonstrated roentgenologically as fluid levels.* Peripheral edema has been attributed to hypoproteinemia. Hotz [4] related dehydration to loss of electrolytes in the feces, and Abicht and Kuhlmann [5] related it to the excess of fluid in the gastrointestinal tract. Wollaeger and Scribner [6] called attention to a delay in the excretion of water with regular nocturnal diuresis in patients with nontropical sprue. Their studies indicated that water is retained in the gastrointestinal tract for long

* References 2 and 3.

periods only when food is present there and suggested that retention of water in the small intestine is somehow of importance to this malfunctioning organ in its digestion or absorption of food. Slowed absorption of water per se may explain retention of fluid in the gastrointestinal tract. The studies of Taylor † indicated that such impairment of absorption of water actually exists in nontropical sprue, a finding which recently has been confirmed by Higgins and his co-workers.‡

Foodstuffs: Absorption of fat, protein, and carbohydrates is significantly disturbed. When patients with nontropical sprue took a standard test diet which provided approximately 102 gm. of fat, 18 gm. of protein, and 270 gm. of carbohydrate, they lost in the feces a daily average of nine times the amount of fat and two times the amount of nitrogen lost by a group of normal persons taking the same test diet.[9] The total solid and caloric contents of the feces also were considerably in excess of the normal.

Losses of water and solids including fat and protein determine the character of the feces. When the disease is mild, or during remissions, fecal values may be nearly normal, and the stools may be normal in number and appearance. Constipation may even be present. During exacerbations or in cases in which the diarrhea is chronic, fecal losses of the various constituents of the diet reach high values, and stools increase in number and in volume, become definitely fatty, and may vary in consistency from soft and mushy to watery. During acute exacerbations, enormous quantities of fluid feces may be passed.

Abnormal amounts of carbohydrates have not been demonstrated chemically in the feces of patients with nontropical sprue or in other types of steatorrhea probably because of the technical difficulties encountered. However, the flat glucose-tolerance curve usually obtained in nontropical sprue is evidence of slowed absorption of glucose. It is possible that unabsorbed carbohydrate accounts for some of the abnormally large quantities of fecal solids and for part of the marked flatulent indigestion present in these cases. Diminished intake of food resulting from the anorexia and abdominal distress experienced by patients with sprue, as well as the large caloric loss in the feces, readily explains the loss of weight which is so prominent a feature of this disease.

Nitrogen balance usually has remained positive with intakes of 11 gm. or more of protein nitrogen per day.[9] This tendency to retain nitrogen is indicative of the chronic protein depletion of patients with this disease. Positive balance apparently may be maintained, except during acute exacerbations, by a high intake of protein. Negative balances have been observed when values for absorbed nitrogen (dietary nitrogen minus fecal nitrogen) fell to about 7 gm. daily during a remission of the disease. The combination of reduced intake resulting from anorexia and fear of eating, the impaired absorption of protein and other nutrients, and the negative nitrogen balance apparently are responsible for the hypoproteinemia and the resulting nutritional edema and ascites. Interference with metabolic processes by the deficiency of other nutrients may likewise contribute.

Electrolytes and Minerals: Fecal values for calcium, phosphorus, chloride, sodium, and potassium[9] vary with the severity of the disease and with the intake but tend to be greater than the average values reported for normal persons. Except for chlorides and potassium, urinary excretion of electrolytes usually has been less than that of normal persons with similar intake. Balances for calcium, phosphorus, chlorides, sodium, and potassium may be negative during acute exacerbations, largely because of abnormally large fecal losses, even when the intake is adequate for metabolic equilibrium in the normal person. Hypochloremia, hyponatremia, and hypokaliemia presumably

† References 7 and 8.

‡ Higgins, J. A.; Lee, P. R.; Scholer, J. F.; Reitmeier, R. J.; Code, C. F., and Wollaeger, E. E.: The Absorption of Water and Sodium from the Small Intestine of Patients with Nontropical Sprue, unpublished data.

follow negative metabolic balances. Defective absorption of calcium may be brought about by a number of factors, such as the combination of calcium with unabsorbed fatty acids to form insoluble soaps, the loss of calcium gathered into the fecal masses, the failure to absorb vitamin D with consequent vitamin D deficiency, and impaired ability to absorb calcium itself. Failure to reabsorb calcium which enters the intestinal lumen in secretions from the liver, pancreas, and intestine appears to be an important factor in producing negative balances. The abnormally large fecal losses of calcium and resulting negative balances explain the hypocalcemia and resulting tetany and osteomalacia frequently seen in this disease. When osteomalacia is present, the chemical changes in the blood characteristic of this disease will be found (low values for serum calcium or phosphate or both, and frequently an elevation of the serum alkaline phosphatase).

Aside from the excessive loss of sodium in the feces, direct evidence of impaired absorption of sodium from the bowel recently has been obtained by using radioactive isotopes.§ Hypokaliemia and clinical depletion of potassium have been demonstrated || repeatedly in nontropical sprue. Blainey and his co-workers,[15] employing the principle of isotopic dilution with radioactive potassium (K^{42}), demonstrated the frequent reduction from normal in total exchangeable potassium in this disease.

Absorption of radioactive iron is impaired[16]; malabsorption of iron may at least partially explain the hypochromic anemia so common in this disease.

Vitamins: Evidences of deficiencies of both water-soluble and fat-soluble vitamins are frequently noted in nontropical sprue. Impaired absorption of the water-soluble B vitamins is indicated by glossitis, stomatitis, cheilosis, and rarely by the appearance of peripheral neuritis in the course of the disease. Occasionally also it may be indicated by the appearance of the megaloblastic type of anemia which responds to folic acid, liver therapy or vitamin B_{12} (impaired absorption of vitamin B_{12} in nontropical sprue has been demonstrated using $CO^{60}B_{12}$).¶ Vitamin C deficiency in the form of frank scurvy has not been observed to our knowledge. A deficiency of vitamin A is sometimes demonstrable by tests for night blindness and very rarely by the presence of xerosis of the conjunctiva. The demonstration of impaired absorption of vitamin A by means of tolerance tests[19] or of its precursor carotene by measuring its concentration in the serum is sometimes helpful in establishing the diagnosis of nontropical sprue. Evidences of vitamin D deficiency frequently are encountered, mainly in the form of tetany and the clinical and chemical manifestations of osteomalacia. These are favorably influenced by large doses of vitamin D and the administration of calcium supplements. Malabsorption of vitamin K manifests itself frequently and definitely as a hemorrhagic diathesis with elevation of the blood prothrombin time, which quickly reverts to normal when suitable preparations having vitamin K activity are administered.

Impaired Motility of Small Intestine.—Roentgenologic studies # of the small bowel disclosed hypomotility and alterations in mucosal relief, especially of the jejunum. The small bowel is dilated; the mucosal markings are thickened; the contours of the lumen are smooth; the usual markings of the valvulae conniventes are obliterated; barium is clumped in elongated masses, and after the bulk of the opaque meal has passed, remnants of barium adhere to the walls, giving it a peculiar flecked appearance. There is evidence of hypersecretion or retention of fluid in the small bowel. These findings suggest that the small bowel

§ Higgins, J. A.; Lee, P. R.; Scholer, J. F.; Reitemeier, R. J.; Code, C. F., and Wollaeger, E. E.: The Absorption of Water and Sodium from the Small Intestine of Patients with Nontropical Sprue, unpublished data. Reference 10.

|| References 11-14.

¶ References 17 and 18.

References 2, 3, and 20

is in essence changed into a flabby, distended tube of varying irregular caliber through which fluid and foodstuffs slowly move without the aid of the usual rhythmic intestinal contractions. These changes may become less marked during remissions of the disease but seldom disappear entirely. Ingelfinger and Moss,[21] in 1943, employing the balloon technique, found evidence of hypomotility and lack of resistance to distention in the small bowel of patients with sprue.

The relation of abnormalities of motility to malabsorption has not been defined. It is possible that disturbed motility may be either the cause or the result of malabsorption or may simply accompany it as an associated manifestation of dysfunction. That changes in intestinal motility may significantly affect the rate of absorption in normal persons has been demonstrated in the case of glucose, methionine,[22] vitamin A,[23] water, and sodium.*

Other Physiologic Abnormalities.—Secretory activity of the stomach is normal in most cases. Cooke[24] found histamine-fast achlorhydria in 20% of his series of patients and hypochlorhydria in a similar proportion. External pancreatic secretion as measured by the secretin test[25] usually is normal, but has been found subnormal in a few cases.[26] Diabetes mellitus has occurred in a few instances, but presumably as an unrelated condition. Hypofunction of the adrenal cortex in nontropical sprue is suggested by the increased melanin pigmentation of the skin, the low blood pressure and the abnormally low excretion of 17-ketosteroids and corticosteroids in the urine.† Such hypofunction can be attributed to malnutrition and is not the primary cause of the disease. The administration of adrenal steroids, although it ameliorates the symptoms and signs of sprue, does not entirely correct them. The cause of mildly elevated basal metabolic rates in some patients is not clearly understood.

Course of the Disease, Physical Findings, and Laboratory Studies

Nontropical sprue usually follows a chronic course with remissions and exacerbations sometimes extending back into childhood (adult celiac disease). Anemia, asthenia, peripheral edema, the bone pains of osteomalacia masquerading as "arthritis" or tetany may be the symptom which brings the patient to the physician, but usually it is fatty diarrhea. The diarrhea may be intermittent at first, sometimes alternating with constipation, but later it becomes continuous. Stools may be watery but often are soft, bulky, frothy, greasy, and light-colored. At times they may appear normal in color and consistency, and in rare instances no history of diarrhea can be elicited. Anorexia, weakness and loss of weight may be severe. Some patients complain of an excessive appetite and fail to gain weight in spite of what they consider to be an excessively large intake of food. Gaseous abdominal distention associated with considerable discomfort is a frequent complaint and is likely to progress in severity as the patient eats his meals during the day. Glossitis and stomatitis are common.

On physical examination emaciation and dehydration, pallor of the skin and mucous membranes, and glossitis with or without patchy atrophy of the tongue are frequently seen, but the most striking feature is the distended, protruding, tympanitic abdomen. Peripheral edema is common, but a detectable degree of ascites is rare. Chvostek's and Trousseau's signs frequently are positive or manifest tetany may be present. In well-developed sprue, generalized brownish-yellow pigmentation may involve especially the creases of the skin of the hands; the distribution of pigment may be suggestive of that seen in Addison's disease. More commonly, the pigmentation affects mainly the exposed surfaces of the skin, and this

* Higgins, J. A.; Code, C. F., and Orvis, A. L.: The Influence of Motility on Rate of Absorption of Sodium and Water from the Small Intestine of Healthy Persons, Gastroenterology, to be published.

† References 6 and 27.

to some extent resembles the skin lesions of pellagra. There may also be a patchy, itching, pigmentary dermatitis. Peripheral neuritis and subacute combined degeneration of the spinal cord are rarely encountered. Evidences of a hemorrhagic tendency, petechiae, ecchymoses, and even bleeding from the orifices may be seen occasionally. Stunting of growth when the onset of the disease dated into childhood and bony deformities are sometimes present. A few patients with advanced osteomalacia and often with pseudofractures may be completely incapacitated and bedridden because of the severe bone pain.‡

Appropriate laboratory tests serve to demonstrate the existence of malabsorption in both mild and well-developed cases. The finding of excessive quantities of fat in the feces is of primary importance, since nontropical sprue is always associated with steatorrhea. When the fat content of the stool is high, gross inspection will disclose its fatty character. Usually in the presence of steatorrhea fat globules will be found on microscopic examination of the feces and can be revealed more strikingly by staining the fecal smear with Sudan III. These are excellent screening procedures, but they are not diagnostic and, therefore, they should be confirmed by more precise quantitative procedures. Quantitative analysis of a single stool collected while the patient is taking a diet low in fat may demonstrate steatorrhea if fat (total lipid) is found to comprise 30% or more of the dry weight of the feces.[28] However, this type of test may give a falsely negative result, since values of less than 30% will sometimes be obtained even in the presence of marked steatorrhea. This occurs when the quantity of nonfatty constituents of the feces is also increased. Chemical measurement of the total daily quantity of fat or nitrogen in the feces is a more dependable procedure. The analysis of all feces passed in 24, 48, or 72 hours (the length of collection depending on the frequency and regularity of bowel movements) may give acceptable laboratory confirmation of malabsorption of fat or protein or both. A fat (total lipid) content of more than 10 gm. per 24 hours when the fat in the diet is relatively low confirms the existence of steatorrhea. Similarly, values for fecal nitrogen of more than 3 gm. per 24 hours indicate azotorrhea. In borderline cases, when the degree of steatorrhea may be minimal, chemical analysis of all feces passed over a period of from three to six days while the patient is ingesting a standard test diet[29] containing approximately 100 gm. of fat per day may be necessary to establish the presence of excessive fat in the stool. Under such conditions, collections usually are started after the patient has ingested the diet for two or three days. Values obtained are compared with those from normal persons ingesting the same diet, the upper limits of normal being, respectively, 7.5 and 2.5 gm. per 24 hours for fats and nitrogen, and 20% for percentage of total fecal solid that is fat. Further evidence of malabsorption is obtained when the curves showing results of the glucose- or vitamin-A-tolerance test are flat and the level of serum carotene is below the lower limit of the normal range (40 units). An elevated prothrombin time indicative of impaired absorption of vitamin K is likewise of diagnostic value.

Appropriate chemical analyses of the blood, serum, or plasma will often give evidence of one or more deficiency states with low values for blood proteins, calcium, phosphorus, sodium, potassium, or chloride. The hemogram and stained smears of the blood reveal anemia, hypochromic, normocytic, or macrocytic as the case may be. In a few cases the peripheral blood picture is indistinguishable from that of pernicious anemia and is associated with megaloblastic bone marrow. In most instances the macrocytes in the peripheral blood are in every way similar to those

‡ Juergens, J. L.; Scholz, D. A., and Wollaeger, E. E.: Severe Osteomalacia Associated with Occult Steatorrhea Due to Nontropical Sprue: Report of 5 Cases, A. M. A. Arch. Int. Med., to be published.

found in patients with liver disease. Although macrocytosis is not invariably present at each examination of patients with nontropical sprue, it occurs at some time during the course of the disease in practically all of them. In most cases the degree of anemia is not great, yet it is frequently resistant to all forms of therapy.

Roentgenologic studies of the small intestine may be of considerable diagnostic value in revealing the so-called "deficiency pattern" (as described in the section on motility) and in ruling out such lesions of the small intestine as enteritis and tumors which can produce a clinical picture closely simulating that of nontropical sprue. Although suggestive of sprue, the deficiency pattern is by no means pathognomonic of this disease, since the same findings have been described in a variety of clinical states. Roentgenographic studies of bone may show evidence of impaired calcification, pseudofractures, or bony deformities characteristic of osteomalacia.

Diagnosis

The diagnosis of nontropical sprue should not be difficult when the clinical picture of malabsorption, of which steatorrheic diarrhea is the most prominent symptom, and the deficiency states which have been described are borne in mind. Its diagnosis rests, first, on demonstration of the several facets of the syndrome (steatorrhea and deficiency states secondary to malabsorption of foodstuffs, electrolytes, and vitamins), and, second, on exclusion of pathologically recognizable entities capable of producing the syndrome.

The sprue syndrome should be suspected in every case of diarrhea, especially if the description of the stools suggests an excessively large bulk or content of fat, and the diagnosis should be pursued if microscopic examination of the feces in the course of a stool test to exclude a parasitic cause for the diarrhea discloses fat in excess. The sprue syndrome should be suspected even more strongly in every case of latent or active tetany, of osteomalacia with bone pain, of dependent edema for which no other cause is found, and of macrocytic anemia in persons whose gastric mucosa secretes free acid and who do not have liver disease; this is especially so if intermittent or chronic diarrhea has been present. The diagnosis should present few difficulties in well-established cases in which diarrhea, obviously fatty in nature, flatulent indigestion, glossitis, stomatitis, latent or active tetany, a protuberant and distended abdomen, vitamin deficiencies (particularly those of vitamins A, B, D, and K), and obvious loss of weight with muscular wasting are present. This is particularly true when characteristic symptoms have been present for several years with periodic remissions.

Differential Diagnosis

With the existence of a sprue-like syndrome once established, organic causes are excluded.

Pancreatic Steatorrhea.—The steatorrhea of chronic pancreatitis usually is recognized without difficulty. The steatorrhea usually develops after years of recurring attacks of abdominal pain characteristic of recurrent acute or subacute pancreatitis. It is a late development which indicates extensive destruction of the pancreas. Concomitantly with the development of steatorrhea, pancreatic calcification or diabetes, or both, appear and serve to locate the pathologic process in the pancreas.[30] In the rare and unusual case of chronic pancreatitis in which progressive destruction of the organ occurs without pain,§ pancreatic calcification or diabetes, or both, also serve to localize the disease process. The steatorrhea of primary pancreatic atrophy and of the rare case of pancreatic carcinoma in which fatty diarrhea is the presenting symptom usually may be differentiated from that of nontropical sprue by the absence of the deficiency states seen in the sprue syndrome. In the differentia-

§ Bartholomew, L. G., and Comfort, M. W.: Chronic Pancreatitis Without Pain, Gastroenterology, to be published.

tion of nontropical sprue from carcinoma of the pancreas, the duration and character of the steatorrheic diarrhea may be of help, because the symptoms of nontropical sprue tend to persist with remissions and exacerbations for many years while those of malignant disease are progressive and almost always terminate fatally within three or four years. The demonstration of impaired external pancreatic function by measurement of the volume, bicarbonate and enzyme contents of the pancreatic secretion, preferably after stimulation of the pancreas by secretion [31] or methacholine (Mecholyl) chloride, may be of diagnostic help in doubtful cases. The effectiveness of pancreatin in the therapy of pancreatic steatorrhea serves further to distinguish the steatorrhea of pancreatic disease from that of nontropical sprue.

In cases in which steatorrheic diarrhea began in infancy, the pulmonary symptoms and findings of fibrocystic disease will usually serve to distinguish it from celiac disease; demonstration of external pancreatic insufficiency confirms the diagnosis. Di Sant'Agnese,[32] in 1956, called attention to the diagnostic importance of a familial occurrence of fibrocystic disease as well as to the excessive loss of sodium and chloride in the sweat of patients afflicted with it.

Nonspecific Granulomatous Gastroenteritis (Regional Enteritis).—Extensive involvement of the small bowel, of the upper part especially, including the duodenum and jejunum, with regional enteritis not infrequently leads to excessive loss of fat in the feces and to deficiency states like those seen in the sprue syndrome.‖ Other mechanisms by which this disease may produce steatorrhea are the formation of enteroenteric fistulas and long-standing partial obstruction of the bowel with impaired function of the distended bowel proximal to the point of obstruction. Careful roentgenologic examination of the small bowel usually will establish the diagnosis and should be carried out in every case of sprue-like syndrome. Fever, abdominal pain, tender masses and fistulas also serve to distinguish regional enteritis from nontropical sprue. Other types of chronic enteritis, particularly tuberculosis, may produce steatorrhea and must be considered in the diagnosis.

Whipple's Disease.—Whipple's disease is a rare condition which produces a sprue-like syndrome. The principal findings are voluminous fatty stools, pigmentation, arthritis, and loss of weight. It may be suspected as the cause of the syndrome when arthritis is associated, and in some instances when an abdominal mass is present. Evidences of pleural and pericardial inflammation with effusion have been noted in some cases. The diagnosis of Whipple's disease may be proved by demonstration of the characteristic microscopic pathologic findings on biopsy of the wall of the small intestine and mesenteric lymph nodes.

Steatorrhea Complicating Diabetes Mellitus with Neuropathy.—Severe, long-standing diabetes mellitus associated with neuropathy [34] sometimes produces a sprue-like syndrome presumably by involvement of the nervous mechanism of control of the intestinal tract. The simultaneous occurrence of lesions of the autonomic and peripheral nerves in a case of long-standing severe diabetes mellitus with fatty diarrhea permits a ready diagnosis. The steatorrhea and the severe, intractable diarrhea do not respond to any form of therapy including strict management for nontropical sprue, nor do they respond to the administration of large doses of pancreatin.

Amyloidosis and Scleroderma.—Amyloidosis occasionally involves the small bowel and produces a sprue-like syndrome. It is suspected when the disease involves multiple organs (heart, liver, skin, intestinal tract, kidneys, and others) and is proved by the Paunz test or biopsy of an involved organ with demonstration of amyloid by the appropriate staining procedures.

Scleroderma is another widespread disease which may occasionally involve the small intestine and cause steatorrhea. Be-

‖ References 24 and 33.

cause of the skin and joint manifestations as well as the evidences of anatomic and functional change in the esophagus, this disease usually is not difficult to recognize.

Deficiency states secondary to operative procedures involving the stomach and small intestine, and strictures and fistulas involving the small intestine may simulate sprue. The history of previous operations, roentgenologic demonstration of a fistula, stricture or short-circuited bowel, or an abnormally short segment of small bowel below a gastroenteric stoma rarely permits confusion as to diagnosis.

Lymphosarcoma and Other Tumors Involving the Small Intestine.—Lesions of this type may produce a clinical picture closely simulating sprue [35] and are not always detectable even on careful roentgenologic examination of the small bowel. The clinical course of patients with such lesions is likely to be more progressive and the response to treatment not as satisfactory as that of most patients with nontropical sprue. On the other hand, temporary responses to medical treatment have been reported in some cases. Most patients with malignant tumors of the small bowel will succumb to their disease well within three years, so that a long history of steatorrhea seems to eliminate them from consideration. In doubtful cases abdominal exploration may be necessary to settle the diagnosis. Lymphosarcoma may produce steatorrhea by blockage of the mesenteric lymphatics as a consequence of involvement of the lymph nodes even when the wall of the bowel is free of disease. Similar lymphatic blockage from tuberculous mesenteric lymphadenitis or other inflammatory or malignant disease is rarely the cause of a sprue-like syndrome.

Tropical Sprue.—It is possible, as some observers believe, that tropical and nontropical sprue are the same disease occurring in different climatic belts of the world. If not identical, they may at least stem from the same basic defect which has been influenced by different environmental factors such as climate and diet. In any event the clinical pictures of tropical and nontropical sprue are in most respects similar. Reports in the medical literature indicate that certain differences exist between them, however. Among these are the following differences.

1. Tropical sprue in some parts of the world has a seasonal incidence and tends to occur in certain geographic regions in the tropics where it may affect many inhabitants at the same time. It often develops in a relatively abrupt manner and runs a rapid course. Nontropical sprue, on the other hand, is less common, occurs sporadically, has no seasonal or geographic incidence, and is usually a chronic and insidious disease.

2. In most cases of tropical sprue reported, a macrocytic anemia indistinguishable from pernicious anemia is present and is associated with megaloblastic bone marrow. Although macrocytic anemia is commonly found in nontropical sprue, it only occasionally presents the characteristics of pernicious anemia and may not be associated with megaloblastic marrow. Perhaps in part at least this difference may be due to the fact that in some series of patients with tropical sprue demonstration of the pernicious anemia type of hematologic change has been considered essential to the diagnosis. In nontropical sprue, on the other hand, more attention has been paid to the demonstration of steatorrhea by careful quantitative analysis of feces for fat as a requisite to the diagnosis.

3. Most patients with tropical sprue give a history of inadequate ingestion of food, particularly of protein. Among patients with nontropical sprue such a history is the exception rather than the rule.

4. Evidences of vitamin D deficiency such as osteomalacia and tetany are rarely reported among patients with tropical sprue but are common in the nontropical variety. The difference has frequently been ascribed to the antirachitic effect of the relatively greater exposure to sunlight of patients living in the tropics.

5. Many reports in the literature indicate that most patients with tropical sprue can be completely cured of their disease by a period of medical treatment including a proper diet and the administration of liver extract, vitamin B_{12}, or folic acid. Although these measures are often helpful to patients with nontropical sprue, they are not curative since some degree of anemia often persists and exacerbations of diarrheic steatorrhea may occur while the patient is under careful treatment. Even when patients with nontropical sprue are enjoying a remission from their disease, careful studies will reveal steatorrhea or other evidences of impaired function of the small bowel. It is possible that patients treated for tropical sprue have not been as carefully checked for evidences of malabsorption after their apparent recovery.

Treatment

Treatment of nontropical sprue over the years has proved difficult. Repeatedly early hopes that a remedy might offer consistently dependable relief have not materialized. Remissions attributable to therapeutic agents currently in vogue have not proved lasting, and exacerbations have continued to occur in most cases. Although some patients who adhere closely to a careful program of treatment may get along satisfactorily for many months or years, intake-excretion studies carried out when they are in remission seldom if ever disclose entirely normal absorption of fat. Also any deviations from the regimen of treatment, particularly dietary indiscretions, are likely to cause a flare-up of symptoms. Our experience has taught us that dependence should not be placed on a single therapeutic measure. Instead, in the absence of a specific remedy, a regimen should be chosen which is based on knowledge of the pathologic physiology of the disease and is designed to avoid irritating or overburdening the malfunctioning bowel, as well as to compensate for malabsorption and to overcome deficiency states. One general measure, which we have found to be of considerable importance in the management of patients with this disease, is avoidance of overexpenditure of nervous and physical energy. Many patients with nontropical sprue are naturally energetic and conscientious and find it difficult to accept the limitations of energy expenditure (especially with regard to the amount of responsibility they assume) which their disease imposes on them. Yet they do best when they recognize these limitations and stay within them. A period of rest in bed during exacerbations of the disease is often helpful in bringing about a remission.

Dietary Measures.—The objective of dietary management is to overcome and avoid malnutrition and the protein, mineral, and vitamin deficiencies. The diet should contain calories, protein, minerals, and vitamins in quantities larger than needed by the normal person to allow for losses in the feces. Such a diet will be high in carbohydrate and protein and should be supplemented by minerals and vitamins. It should be low in fat to avoid the irritating effects which even moderate amounts of fat produce on the gastrointestinal tracts of patients with this disease. The restriction of dietary fat often will result in quick and striking relief of symptoms, particularly the diarrhea and abdominal distress. Anorexia and capriciousness of appetite require that the diet be pleasing to the eye, palatable to the taste, and tailored to the likes and dislikes of the patient.

The dietary program which we have used consists of a foundation diet and a full diet.[36] The foundation diet provides 130 gm. of protein, 55 gm. of fat, and 370 gm. of carbohydrate with 2500 Cal. It also contains 1780 mg. of calcium, 18 mg. of iron, and meets the recommended daily allowances of the National Research Council for all vitamins except vitamin A. The full diet provides 130 gm. of protein, 70 gm. of fat, 400 gm. of carbohydrate, and 2750 Cal. and meets the recommended allowances in every respect. In general, the diet is low in fat and high in protein, carbohydrate, and Calories, and the amount of

residue is restricted. A large proportion of the carbohydrates used are those from fruits and simple sugar, fructose and glucose. The diet is varied with the person; in some cases even the foundation diet will require alteration. In others the physician may order additions to increase the calories by increasing the fat and starch allowed, especially during remissions. In general, patients use the foundation diet during exacerbation of their disease, and additions to the diet can be made one at a time as clinical improvement occurs until a full sprue diet is being taken.

Gluten-Free Diet.—The observation of Dicke,[37] in 1950, that children with celiac disease improved when wheat flour and rye flour were excluded from their diets, and that of Weijers,[38] also in 1950, that fecal fat decreased when these flours were excluded from the diet have altered the therapy of celiac disease. These observations were confirmed in respect to wheat flour by Anderson and associates[39] in 1952 and Sheldon and Lawson[40] in 1952. The harmful substance was found in the gluten fraction of wheat flour by Anderson and associates[39] in 1952 and in the gluten fraction of wheat and rye flour by van de Kamer, Weijers, and Dicke ¶ in 1953. Gerrard, Ross, Smellie, and associates # confirmed the beneficial effect of restriction of flour in 1955. The clinical similarity, if not actual identity, of celiac disease and nontropical sprue induced Anderson and associates[45] in 1954 to treat nontropical sprue similarly. They reported that five of 12 patients with nontropical sprue apparently returned to normal health on a wheat-free diet in two months. Diarrhea stopped, the color of the stools became darker, appetite improved, weight increased, and loss of fecal fat diminished. Macrocytosis was corrected, and the blood picture became normal. Reintroduction of wheat protein into the diet in three cases led to deterioration of the condition. The remaining seven patients did not respond favorably to the treatment. Ruffin, Carter, Johnston, and Baylin[46] in 1954 reported that a wheat-free diet had caused remission in three patients, and Mortensen[47] in 1955 reported a remission in a single patient with sprue. Encouraging results have been obtained in a few patients treated at the Mayo Clinic, but there have also been failures. These experiences suggest the need for a critical trial of the gluten-free diet. In a disease like nontropical sprue which has spontaneous remissions and which usually responds satisfactorily to the time-tested sprue diet outlined, it may not be easy to evaluate this new diet or to demonstrate its superiority over diets now commonly in use. Since the gluten-free diet imposes considerable restriction on the patient and entails the use of special recipes for wheat and rye substitutes, superiority must be clearly demonstrated before the diet can be prescribed routinely for all patients with nontropical sprue. It may be found useful in the treatment of certain patients who do not respond favorably to the usual measures.

Vitamin Supplements.—Each patient should receive at least one multiple vitamin capsule daily. If evidence of vitamin deficiencies exists, large additional doses of the several vitamins may be given. Vitamin A in doses of 50,000 I. U. daily is indicated in the presence of keratosis pilaris (perhaps a vitamin A deficiency), xerosis conjunctivae, and night blindness. Vitamin D in doses of 25,000 to 50,000 I. U. daily is added when hypocalcemia, osteomalacia, and tetany are problems, and if hypocalcemia is refractory doses up to 300,000 or 400,000 I. U. daily may be given to increase absorption of calcium. Although water-miscible preparations of vitamin D are probably more readily absorbed from the gastrointestinal tract than oily ones, the latter are effectual if given in sufficiently large doses and are preferable from the standpoint of cost and conveniences of administration. In patients without clinical evidence of osteomalacia 5000 to 10,000 units per day is indi-

¶ References 41 and 42.
# References 43 and 44.

cated as a prophylactic measure. Water-soluble preparations having vitamin K activity, given orally in doses of 4 mg. per day, will usually rapidly correct a hemorrhagic tendency and return the prothrombin time to normal. On rare occasions 8 or 12 mg. per day by mouth have been required to accomplish this result, but we have never found it necessary to administer vitamin K parenterally except when vomiting prevented oral administration. As a prophylactic measure doses of 4 mg. given at daily to weekly intervals depending on the magnitude of the absorption defect are useful in preventing hypoprothrombinemia. The vitamin B complex will be given in large doses to patients with peripheral nerve lesions, pellagrous skin lesions and glossitis. Liver extract, pteroylglutamic acid, or vitamin B_{12}, given parenterally, is indicated in cases with macrocytic anemia. The response in the patients with severe anemia of the pernicious anemia type and megaloblastic bone marow will sometimes be striking, but treatment usually exerts little effect on the mild macrocytic anemias or on the size of the erythrocytes. These hematopoietic agents have no demonstrable effect on the steatorrhea of nontropical sprue.

Minerals and Electrolytes.—Because of the frequency with which osteomalacia develops in nontropical sprue, the oral administration of calcium lactate in doses of 4 gm. (1 dram) three times per day along with suitable prophylactic doses of vitamin D is recommended for all patients. For patients with known osteomalacia larger doses of calcium lactate, as high as 12 gm. (3 drams) three times per day and even higher and also larger doses of vitamin D are necessary. For the treatment of active tetany the intravenous use of calcium gluconate is helpful.

The frequency of potassium deficiency and the probability that hypokaliemia is one of the common causes of death in nontropical sprue[24] emphasize the need for adequate replacement therapy by the oral and, if necessary, by the intravenous route during episodes of diarrhea. Intravenous infusions of 5% dextrose in isotonic saline solution are helpful in the management of patients with water and electrolyte imbalance associated with exacerbations of the disease.

Iron deficiency anemias when present can sometimes be corrected by the oral administration of ferrous sulfate or other iron-containing compounds. However, many patients do not tolerate such medication, and in those who do the response of the anemia to their administration is often disappointing. Even when iron is administered parenterally, the anemia of some patients thought to be due to iron deficiency is not corrected. On occasions blood transfusions are helpful in controlling intractable anemia and severe hypoproteinemia or in rehabilitating seriously ill patients. The experience of one of us (Wollaeger) and that of others[48] have shown that intravenous injections of human serum albumin will restore serum protein levels to normal. Although the effects are often temporary, the administration of serum albumin in some instances has seemed to improve the patient's general condition and bring about a remission of symptoms which has persisted for long periods. This type of therapy has also been of use in the control of severe and persistent tetany which does not respond readily to the administration of large doses of calcium and vitamin D.*

Steroid Therapy.—Cortisone, hydrocortisone, and their analogues, prednisone and prednisolone, as well as corticotropin (ACTH) exert a beneficial effect when administered to patients with nontropical sprue in relapse.† Both subjective and objective improvement are observed. Stools decrease in number and become more normal in consistency; appetite and strength improve, and symptoms of abdominal cramping and distention become less marked or even disappear. The amounts of solids, water, fat, and nitrogen in the feces de-

* Reference 49; Wollaeger, E. E., unpublished data.

† References 27 and 49.

crease, and the prothrombin time returns to normal. Fecal loss of potassium is decreased, but its urinary excretion is increased, and the serum level may be further depressed. Sodium and chloride are retained at least initially during treatment with cortisone with increased positive balances and elevation of serum values. Rebound occurs when the use of cortisone is discontinued. Values for serum calcium may increase toward normal; fecal losses may decrease, and positive balance may be exhibited, but in some cases hypocalcemia has become more marked in spite of treatment with hormones, indicating the necessity of continuing administration of calcium and vitamin D as an adjunct to cortisone therapy. The improvement observed would seem attributable in large part to more efficient intestinal absorption, although some of it can probably be ascribed to better systemic metabolism. Untoward symptoms, including hypertension and edema, occur when the hormone is given in large doses.

Our experience with steroid therapy in nontropical sprue has been confined almost exclusively to the use of cortisone acetate administered orally—a route which has been found more effective than parenteral injection. Cortisone is not used to replace the usual methods of treatment, such as diet, rest, and the administration of vitamins and minerals, but rather to supplement them and help establish a remission in patients who are severely ill and whose symptoms do not respond readily to ordinary measures. The starting daily dosage is generally 100 mg. given in four doses of 25 mg. each. After one to three weeks, the time depending on the clinical response, the total daily dose of cortisone is gradually reduced over a period of one to four months, with the objective of discontinuing its use entirely as soon as possible. The cortisone is administered in three or four doses per day with the intervals between doses as long as the waking hours permit. Total daily dosage is reduced by decrements of 12.5 to 25 mg. per day and in the lower-dose ranges by amounts even smaller than these. In this manner satisfactory remissions can be established and maintained in a great majority of patients who receive this form of therapy; only a few have required maintenance doses of from 12.5 to 25 mg. per day over much longer periods. Thus the patient is spared the dependency on cortisone which results when high-level dosages are maintained over long periods, the invariable relapse which occurs when treatment is discontinued, and the troublesome and sometimes dangerous side-effects of prolonged high dosage. Repeated short courses of cortisone may be used for subsequent relapses of the disease if necessary.

Summary

Nontropical sprue is a disease occurring in adults living in temperate climates in which absorption from and motility of the small bowel are impaired. The etiology is unknown and it does not produce specific anatomicopathologic changes. Nontropical sprue includes celiac disease when it persists into adult life.

Impairment of absorption in nontropical sprue, contrary to early belief, affects all nutrients, including fat, protein, carbohydrate, vitamins, minerals, and even water. Impaired absorption causes deficiency states which together with the symptoms and signs of impaired intestinal function constitute the essential clinical features of the disease. The diagnosis of nontropical sprue rests, first, on demonstration of malabsorption with its associated deficiency states, and, second, on the exclusion of specific pathologic abnormalities that may also produce the syndrome.

Therapy, until a specific remedy is discovered, must be directed toward control of malnutrition and correction of the several deficiency states. The corticosteroids and a gluten-free diet are promising adjuncts to standard forms of therapy.

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Case Reports

THROMBOTIC THROMBOCYTOPENIC PURPURA DIAGNOSED BY RANDOM LYMPH NODE BIOPSY

DENNIS A. J. MOREY, M.D.
JAMES B. WHITE, M.D.
and
WILLIAM M. DAILY, M.D., McKinney, Texas

A CASE OF thrombotic thrombocytopenic purpura is presented in which the diagnosis was established histologically premortem by random lymph node biopsy and sternal marrow biopsy.

Report of Case

A 33-year-old Negro man, a common laborer, was admitted to the Orthopedic Service of the McKinney Veterans Administration Hospital on Oct. 26, 1955, complaining of back pain associated with progressive stiffness over a three-year period. Upon admission he appeared to be healthy except for marked limitation of movement of the entire vertebral column and limitation of expansion of the thoracic cage to ¼ in. (0.6 cm.). X-rays confirmed a diagnosis of extensive rheumatoid spondylitis. Upon admission his hemoglobin was 13.5 gm. per 100 cc.; hematocrit 41%; WBC 5150, with 53% neutrophiles, 40% lymphocytes, 6% monocytes, and 1% eosinophiles. The urinalysis revealed normal findings except for 1+ sugar. Serologic tests for syphilis were negative. The fasting blood sugar was 99 mg. per 100 cc., the two-hour postprandial blood sugar, 106 mg. per 100 cc. He was treated with physiotherapy and 1 tablet of Pabalate (contains 5 grains. [0.3 gm.] each of *p*-aminobenzoic acid and sodium salicylate) q. i. d., but no other medications. Even in retrospect, nothing in his findings or course during the first 23 days in the hospital gave any hint of the catastrophic turn his illness shortly would take.

Submitted for publication May 21, 1956.

Staff Physician, Department of Internal Medicine (Dr. Morey), Resident in Pathology, Department of Pathology (Dr. White), and Chief, Medical Service, Department of Internal Medicine (Dr. Daily), VA Hospital, McKinney, Texas, and the Southwestern Medical School of the University of Texas, Dallas, Texas.

The patient left the hospital on pass on Nov. 18, 1955, the 24th hospital day. En route home he became weak, dizzy, and nauseated and sweated profusely. Shortly after arriving home he vomited without hematemesis and fainted. Then he suffered diarrhea without melena. On the following day extreme weakness and diarrhea persisted, and he fainted twice more. He thought that his urine had become red. He was then returned to this hospital.

On readmission he was afebrile, alert, and cooperative, but complaining of weakness and faintness. The pulse was 110, blood pressure, 112/68. Tenderness was elicited over the left costovertebral angle. The hemoglobin was found to have fallen to 4.6 gm. per 100 cc. The RBC was now 2,030,000; WBC, 11,700, with normal differential. The stools contained neither gross nor occult blood, and the urine was negative except for 1+ protein. In concern that he might be bleeding internally, 3 pt. (1500 cc.) of blood was infused on Nov. 21, 1955. Following the transfusions the hemoglobin was 7.4 gm. per 100 cc.; RBC, 2,500,000; WBC, 9600; platelet count, 48,000. The blood film revealed marked anisocytosis, poikilocytosis, basophilic stippling of erythrocytes, numerous spherocytes, and 20 nucleated RBC per 100 WBC. On this date the patient had the first of many grand mal epileptic seizures. Another pint (500 cc.) of blood was infused. A medical consultant discovered scleral icterus in addition to the previously noted findings, but was unable to feel the spleen.

Upon transfer to the Medical Service, reevaluation established that this patient had developed a severe hemolytic anemia with hemolytic icterus. Evidence for the hemolytic character of the anemia was as follows: Although there was no blood loss, the anemia could be only very incompletely restored by a total of 10 pt. (5 liters) of blood given during his final two weeks of life; the serum bilirubin was 2.75 mg. per 100 cc.; the reticulocyte count, 9.6%; there were numerous nucleated RBC's, and the two-hour urine urobilinogen was 15.3 Ehrlich units. Thrombocytopenia was constant throughout the last week, with platelet levels of 48,000 on Nov. 21, 14,000 and 6000 on Nov. 26. On Nov. 28, 1955, following one direct transfusion and two indirect transfusions, using silicone-coated glassware, the platelet level rose to 68,000

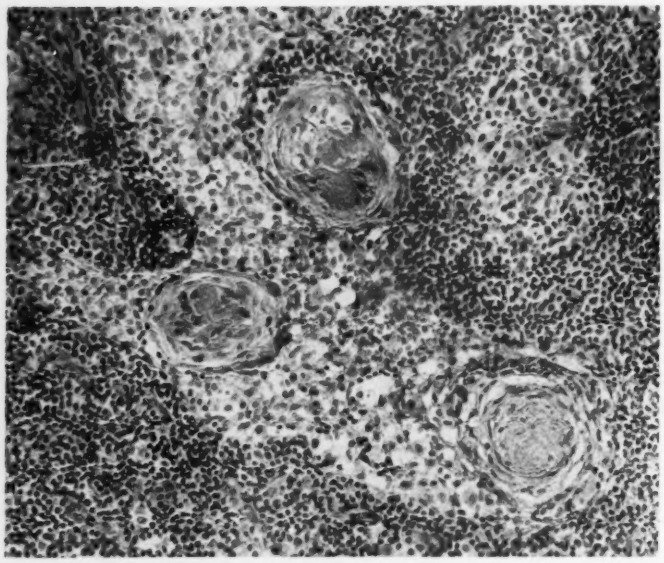

Fig. 1.—Lymph node showing intraluminal occlusive hyaline material.

per cubic millimeter. The erythrocytes did not sickle. The bone marrow revealed moderate erythroid hyperplasia. The blood was negative for cold agglutinins. Both the direct and indirect Coombs' tests were negative. The osmotic fragility of the RBC's was normal. Spinal puncture was attempted but was unsuccessful due to calcification of the interspinous ligaments.

On Nov. 23, 1955, the 29th hospital day, the patient experienced the second severe grand mal seizure, which was followed by delirium lasting 24 hours. Diphenylhydantoin (Dilantin), 0.1 gm. q. i. d., was instituted. On Nov. 26, 1955, convulsions recurred, and thereafter were frequent despite frequent injections of barbiturates. From the onset of these frequent convulsions until death he remained comatose, with generalized hyperreflexia, hypertonia, and bilateral Hoffman and Babinski reflexes. Large hemorrhages appeared in both optic fundi. From Nov. 26, 1955, cortisone in doses of 400-500 mg. per day was administered for the remainder of the patient's life without effect on

Fig. 2.—Low power, same as Figure 1.

Fig. 3.—Section of bone marrow revealing intraluminal occlusive hyaline material.

the thrombocytopenia or neurologic state. In this desperate state splenectomy was seriously considered but was deferred because of a strong clinical suspicion that the patient's disease was thrombotic thrombocytopenic purpura.

On Nov. 26, 1955, at the suggestion of Dr. E. E. Muirhead, a 1 cm. inguinal lymph node selected at random was biopsied for the express purpose of trying to establish this diagnosis. Surgical biopsies of the sternal marrow and of the skin also were done. Histologic examination revealed occlusive hyaline material within the lumina of the small vessels of the lymph node and to less extent in the bone marrow, diagnostic of thrombotic thrombocytopenic purpura (Figs. 1, 2, and 3). The skin biopsy was negative. Thereafter the patient remained comatose and convulsed frequently until his death, on Dec. 2, 1955. Permission for autopsy could not be obtained.

Comment

In the presence of hemolytic anemia, thrombocytopenia, and severe cerebral dysfunction, it is not difficult to entertain the diagnosis of thrombotic thrombocytopenic purpura; however, to establish such a diagnosis unequivocally histologic evidence is required.

Previously, the antemortem diagnosis of thrombotic thrombocytopenic purpura has been established by splenectomy or by isolating vessels in bone marrow aspirate with characteristic lesions.* The frequent finding of such lesions in lymph nodes at autopsy [2] suggested that even random lymph node biopsy during life might yield tissue of diagnostic histology. The rich yield of typical lesions in a single, randomly chosen, small node in this case suggests that lymph node biopsy, here applied for the first time to our knowledge, should have increased application in the antemortem diagnosis of thrombotic thrombocytopenic purpura.

* References 1 and 2.

Summary

A case of thrombotic thrombocytopenic purpura is reported in which the antemortem diagnosis was confirmed by lymph node biopsy. It is suggested that in the presence of the triad of hemolytic anemia, thrombocytopenia, and cerebral dysfunction, the use of lymph node biopsy may prove valuable in establishing a diagnosis of thrombotic thrombocytopenic purpura.

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Books

EDITED BY WILLIAM B. BEAN, M.D.

BOOK REVIEWS

Mitral Stenosis: A Follow-up of 35 Patients. By Knud Henning Olesen. Translated from Danish by Axel Andersen. Price, 18.00 k. Pp. 228, with 110 illustrations. Ejnar Munksgaards Forlag, Nørregade 6, København, K, 1955.

The intelligent selection of patients for mitral valve surgery and the task of evaluating the results of such treatment must depend ultimately upon a clear understanding of the natural history of the disease. Unfortunately, the literature contains relatively little information on the long-term course and prognosis of mitral stenosis other than those studies based upon autopsy series. The purpose of this book is to present the results of a clinical investigation of 351 patients with mitral stenosis; it consists of documentations of the fate of these patients after the initial diagnosis, as well as follow-up examinations of survivors after a period of three to twenty years.

Detailed information on the clinical and laboratory findings at the time of the first examination is given. Although an attempt was made to include only those patients with predominant mitral stenosis, approximately one-fourth of the patients apparently had some mitral insufficiency as well.

The electrocardiographic data consist largely of notations on the cardiac mechanism and on the changes in the T-waves relative to the QRS axis. It is unfortunate that information concerning ventricular hypertrophy is not given on these cases. These objections, however, do not detract from the exhaustive analysis of the cases and the correlation of changes in cardiac status with prognosis. The author has shown that in the majority of cases mitral stenosis is a progressive disease and that the over-all mortality is very high (as high as seventy per cent for pure mitral stenosis during the three- to twenty-year period, but again the need is emphasized of considering each case individually, since those patients in Class II, with sinus rhythm, had a median survival time of over twenty years.

This study is a worthy contribution to our knowledge of mitral stenosis.

E. O. THEILEN, M.D.

Lehrbuch der speziellen pathologischen Anatomie. By Dr. Edward Kaufmann. Edited by Dr. Martin Staemmler. Price, $3.50. Pp. 412, with 192 illustrations. Walter De Gruyter & Company, Berlin, 1954.

I have been handicapped by the fact that only pages 321-412 came into my hands. These pages contain the end of the description of the circulatory system (M. Staemmler) and of the malformations of the heart and the great blood vessels (W. Doerr). The latter chapter represents an entirely new addition to the former book, and it has been written by one of the outstanding experts in his field in a clear, concise style. The available illustrations are satisfactory. Paper and print are very good.

E. STERN, M.D.

1956 Medical Progress: A Review of Medical Advances During 1955. Edited by Morris Fishbein, M.D. Price, $5.50. Pp. 389, with illustrations. McGraw-Hill Book Company, Inc., 330 W. 42d St., New York 36, 1956.

This is the fourth volume in a series designed to review the progress made in medicine during the preceding year. It is literally impossible for us to keep up with everything, and books of this kind are of most value for us to survey what goes on in fields other than our own, or if foreign and out-of-the-way papers are reported. The different chapters in this volume seem to be written without any common pattern. Certainly there is no uniform approach, and they are somewhat uneven. A real contribution of a volume of this kind would be to have entire rather than partial references in which the authors' names and titles as well as the journal, volume, date, and year are indicated. As one

reads from page to page in different sections, one is struck with the enormous number of names of drugs, which adds so much to the confusion in the already complicated field of therapy. Since it is neither a critical nor an analytical review, this book serves its major purpose by calling attention to work which may have been missed. It is a guide rather than an interpretation.

WILLIAM B. BEAN, M.D.

Ergebnisse der medizinischen Grundlagenforschung. Vol. I. Edited by K. Fr. Bauer. Price, $30.70; 129 DM. Pp. 855, with approximately 215 illustrations. George Thieme Verlag, Herdweg 63, (14a) Stuttgart N, 1956.

K. Fr. Bauer, the editor-in-chief of this Volume I, has made a successful attempt to furnish a survey of the results of research in a great variety of specialties during the last five or six years. This book offers an excellent orientation in the state of research in many fields of medicine. It so eliminates the necessity to study the abundance of original papers in spheres foreign to the average reader.

The following are a few of the many chapters dealt with in his work: "The Surface Structures of Bacteria" (J. Tomcsik), "Metabolites and Antimetabolites" (J. C. Somogyi), "Results of Vitamin Research During the Years 1950-1954" (W. Stepp), "The Present Position of Research in Allergy" (F. Scheiffarth), "The Development of the Human Cerebral Cortex" (V. G. Bonin), "The Essential Amino Acids" (J. Kapfhammer, F. Bauer, and V. Kapfhammer), "Embryology in the Service of Research in Disease" (G. Toendury). It is quite impossible for any reviewer to do justice to a book of this scope. It would require a truly encyclopedic knowledge of the entire territory covered. It is exactly this type of knowledge, however, for which this work tries to lay the foundation. Paper, print, and illustrations are of excellent quality in the usual Thieme fashion.

The only (very minor) flaw I was able to detect is a marginal note by Stepp stating that "riboflavin is the name for aneuria (thiamin) in all the Anglo Saxon countries."

E. STERN, M.D.

Laboratory Tests in Common Use. By Solomon Garb, M.D. Price, $2. Pp. 160. Springer Publishing Company, 44 E. 23d St., New York 10, 1956.

This excellent text, written primarily for the nurse, nurse's aid, medical secretary, and office assistant, summarizes simply and concisely most of the commonly used laboratory tests. The procedures are grouped according to the specimen employed, and the reason for ordering each test, procedure for collecting the specimen, technique, and normal values are indicated. In addition, the tests are tabulated according to the organ or system examined.

The book provides a wealth of necessary information for the nurse and nonprofessional physicians' assistants. It represents, however, a marked oversimplication of the field of clinical pathology, and this materially reduces its direct value to the physician, medical student, and trained medical technologist. The book should contribute considerably to a better understanding of laboratory tests by the nurse, secretary, and other related assistants and lead to better rapport between them and the physician.

FRANCIS J. TENCZAR, JR., M.D.

Respiratory Problems in the Premature Infant. Report of the Fifteenth M&R Pediatric Research Conference, Benjamin Kagan, M.D., Chairman. Price, not given. Pp. 87, with illustrations. M & R Laboratories, Columbus 16, Ohio, 1955.

Approximately 14% of premature infants die during the first year of life, and most of these deaths are due to respiratory problems. This monograph deals with many phases of the problem. The following papers plus discussion of each are included: "Uterine and Placental Circulation," by Dr. Elizabeth M. Ramsey; "Hemodynamic Changes in the Fetal Circulation," by Dr. S. R. M. Reynolds; "Tissue Metabolism in Fetus and Newborn Infant," by Claude A. Villee; "Physiology of Initiation and Continuation of Breathing After Premature Birth," by Dr. James L. Wilson; "Gross and Microscopic Changes," by Dr. Edith L. Potter; "Pulmonary Physiology," by Dr. Charles D. Cook; "Obstetrical Factors Influencing Respiratory Difficulties in the Premature," by Dr. Lloyd V. Shields; "Pediatric Factors in Prevention and Diagnosis," by Dr. Steward H. Clifford; "Narcosis and Stimulation," by Dr. John Adriani; "Assisted Initiation and Maintenance of Respiration," by Dr. Richard L. Day; "Immunity," by

Dr. Joseph Dancis; "Antimicrobial Therapy," by Dr. Benjamin M. Kagan; "Nursing Care," by Miss Evelyn Lundeen.

The conference emphasized the fact that there is still a great deal to learn about respiration in the newborn. The exact mechanism for initiation of breathing is unknown, hyaline membrane syndrome is recognized but poorly understood, and some of the factors leading to premature birth of the infant remain obscure. This pamphlet does bring together much of the present knowledge on the subject. Copies can be had by writing to M & R Laboratories, Columbus 16, Ohio.

GEORGE BEDELL, M.D.

BOOKS RECEIVED

Säuglings-Enteritis. Edited by Prof. Dr. A. Adam. Several contributors. Price, $14.30 (DM 60—). Pp. 534, with 43 illustrations. Georg Thieme Verlag, Herdweg 63, (14a) Stuttgart N.; Intercontinental Medical Book Corporation, New York 16, 1956.

Venous Return. By Gerhard A. Brecher, M.D., Ph.D. Price, $6.75. Pp. 148, with 55 illustrations. Grune & Stratton, Inc., 381 Fourth Avenue, New York 16, 99 Great Russell Street, London, W. C. 1, 1956.

J. A. M. A. Clinical Abstracts of Diagnosis and Treatment. By American Medical Association. Price, $5.50. Pp. 661, not illustrated. Grune & Stratton, Inc., 381 Fourth Ave., New York 16, N. Y.; Intercontinental Medical Book Corporation, New York 16, 1956.

News and Comment

ANNOUNCEMENTS

Western Society for Clinical Research.—The 10th annual meeting of the Western Society for Clinical Research will be held Thursday afternoon, Friday morning, and Saturday morning, Jan. 31 through Feb. 2, 1957, at Carmel-by-the-Sea, Calif.

Information regarding the meeting may be obtained from Arthur J. Seaman, M.D., Secretary-Treasurer, Western Society for Clinical Research, University of Oregon Medical School, Portland 1, Ore.

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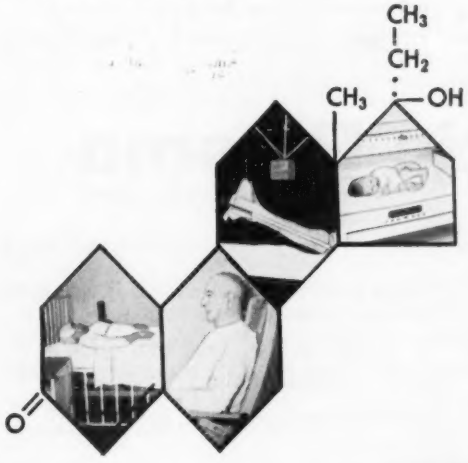

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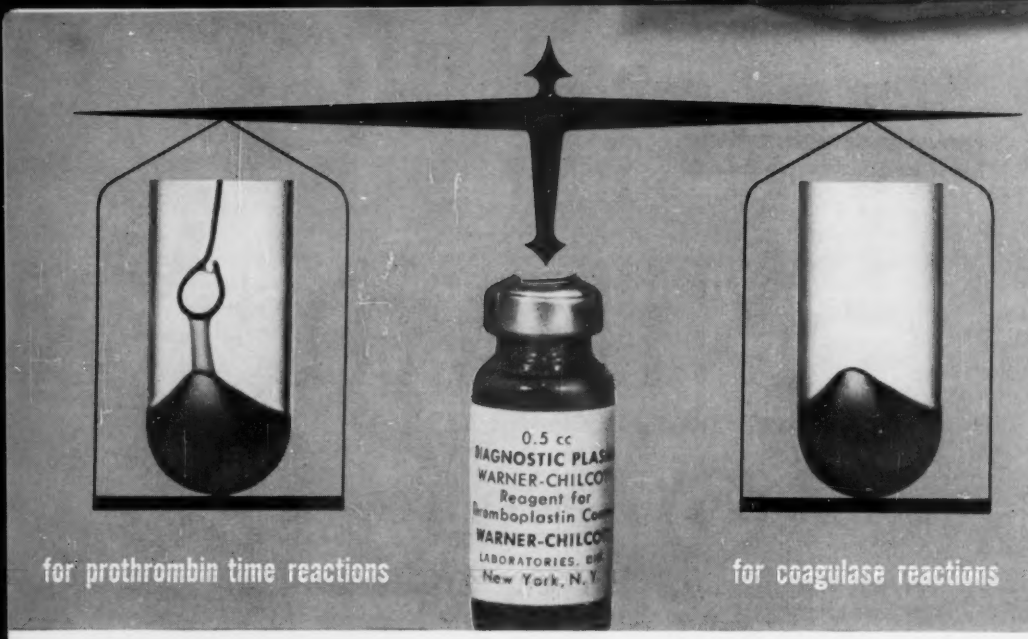

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1. Watt, B.K., and Merrill, A.L.: Composition of Foods—Raw, Processed, Prepared—Washington, D.C., United States Department of Agriculture, Agricultural Handbook No. 8, 1950.

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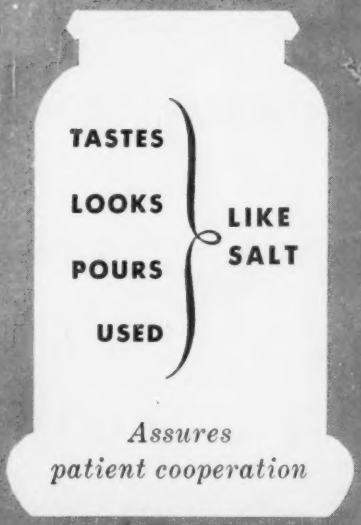

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*Schwimmer, D.; Boyd, L. J., and Rubin, S. H.: Bull. New York M. Coll. 16:102, 1953.

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Sokoloff, O.J.: A.M.A. Arch. Dermat. In press.

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Thimann, J. and Gauthier, J.W.: Quart. J. Stud. Alcohol. **17**: *19, 1956.*

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Borrus, J.C.: J.A.M.A. **157**: *1596, 1955.*

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Selling, L.S.: J.A.M.A. **157**: *1594, 1955.*

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1. Howell, T.H., et al.: Practitioner *173*:172 (Aug.) 1954.

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